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ESSENTIALS OF PHYSIOLOGY

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BAINBRIDGE & MENZIES' ESSENTIALS OF PHYSIOLOGY

SIXTH EDITION

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PREFACE TO THE SIXTH EDITION

THE rapid progress made of recent years in Physiology and Biochemistry has necessitated considerable rearrangement of this textbook. New chapters have been written on Basic Principles, Muscle, Nerve, the Central Nervous System, Vision, Hearing, the Liver, Exercise and Work. New sections have been added on Capillary Circulation, the Vitamins and the Kidney, etc.

In dealing with the Central Nervous System, my aim has been to deal with the physiological rather than the anatomical aspect. I have tried to describe what the various parts do rather than where they are. I have endeavoured to avoid confusing words such as afferent and efferent, and to write clearly on a difficult subject where I feel clarity to be much needed. I hope I have made a judicious blend of older and newer work without disparaging the former or exaggerating the latter. Many old diagrams have been omitted and new ones added. I would like to make special reference to those on the Central Nervous System. I have spent much time on the index in an endeavour to make it useful and efficient. Items in heavy type refer to chapters or important parts of chapters. Numbers in heavy type give the page of principal reference. Pages and references of less importance are in ordinary type. These have been my ideals, but I do not flatter myself that I have achieved them. I am sure that every student will detect mistakes, and that my contemporaries will easily discover many places where improvements in matter and style are needed. When they feel so inclined, I hope they will point them out to me.

Now I want to mention by name those who have helped me. Miss Margaret Watson for her typescript and much sound advice. Messrs. T. P. Collings & Co. for their excellent drawings, and my colleagues, Dr. Gordon Reeves and Mr. F. Haynes, for their many valuable suggestions.

HAMILTON HARTRIDGE.

March 1929.

PREFACE

Our object in writing this book has been to bring together in a concise form the fundamental facts and principles of Physiology, primarily with the object of meeting the requirements of the medical student preparing for a pass examination in the subject of Physiology. Considerations of space have led us to exclude as far as possible histological details and descriptions of chemical and experimental methods which form part of each student's laboratory course, and for which separate text-books are used. We have also omitted, for the same reason, all matter of purely historical interest.

In view of the transitional state of anatomical nomenclature, we have, after much consideration, retained the terminology hitherto used in this country, and have inserted the Basle nomenclature in brackets.

While it is impossible to mention all the sources upon which we have drawn, we wish to acknowledge our especial indebtedness to Prof. E. H. Starling, not only for permission to use many figures from his *Principles of Physiology*, but also for advice and information on many points. Our thanks for permission to use figures, which are as far as possible separately acknowledged in the text, are also due to Prof. Sir E. Sharpey Schafer (*Quain's Anatomy and Essentials of Histology*), Professor J. N. Langley (*Journal of Physiology*), Dr. M. S. Pembrey (*Practical Physiology*), J. Barcroft, Esq. (*Respiratory Function of the Blood*), Dr. A. Hurst, Dr. Homans, Dr. W. E. Hume, Professor R. Howden (*Gray's Anatomy*), and the Council of the Royal Society. We must also thank the Publishers and others who have kindly supplied us with blocks, namely, Messrs. J. & A. Churchill, Hodder & Stoughton, Macmillan & Co., Ltd., Mr. Edward Arnold, the Cambridge University Press, Messrs. Baird & Tatlock, Ltd., and Messrs. Hawksley.

Finally, we are indebted to Miss F. H. Miller for her unwearying efforts in the production of the original illustrations, and to Messrs. Longmans, Green & Co. for the great pains they have taken in the reproduction of the figures.

F. A. BAINBRIDGE.
J. ACWORTH MENZIES.

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ESSENTIALS OF PHYSIOLOGY

CHAPTER I

BASIC PRINCIPLES

SECTION I

THE CELLULAR CONSTITUTION OF THE BODY.—If we examine microscopically the composition of a small portion of the human body we find that it is invariably composed of cells, or the products of cellular activity, or both. If, for example, we took such an unlikely structure as bone for examination, we should find living cells present in it, and, if we watched its growth, we should find that it was produced by living cells. Enamel of teeth, even, has a cellular origin. Suppose that we compare a number of such cells collected from various parts of the body, *e.g.* skin, gland, blood, muscle, etc., we should observe in each case the presence of cells and we should note that these cells had a number of features in common. Practically all the cells would be found to contain a nucleus, the single exception to this being the red blood-corpuscle. Most of the cells, moreover, would have definite cell walls. We are justified, then, in referring to such a thing as a typical cell and a description of the histological features of such a structure will now be given.

HISTOLOGICAL FEATURES OF A CELL.—Cells unmodified by the pressure of their neighbours are usually spherical in shape. They consist externally of a structureless cell membrane; inside this is a mass of protoplasm, which may show no structure whatever or in certain circumstances may exhibit very fine mesh-like structure. Within this protoplasm there may be granules, which by chemical methods can be proved to consist of definite chemical substances, for instance stores of food, *e.g.* fat or glycogen; or secretory products, *e.g.* ferments produced by the activity of the cell; or excretory products which in due course are to be expelled.

THE NUCLEUS is a highly important structure found in the interior of the protoplasm, without which cells probably cannot live long and most certainly cannot reproduce themselves by division. This process, we shall see later, commences by a division of the nucleus which is subsequently followed by a division of the rest of the cell. The nucleus consists of a roughly spherical mass of protoplasm. It is surrounded by a membrane called the nuclear sac. This contains a more fluid portion called nuclear sap, and a more solid portion, *linin*, which has attached to it masses of a substance, *chromatin*, which stains deeply with most basic dyes. Inside the nucleus there is usually one and there may be more structures called *nucleoli*. Occasionally these are colourless but more often they are darkly-staining. Another important constituent of the cell is known as the *attraction sphere* or *astral sphere*. It consists of a minutely granular sphere, the central granule or *centrosome*, from which, during mitotic division, radiate a series of astral rays. In addition, the protoplasm of a cell may be shown to contain minute structures called *mitochondria*. They are found to be essential constituents of practically all cells. Certain investigators ascribe heredity to them.

HISTOLOGY OF SPECIAL CELLS.—The cells met with in the human body differ considerably in size, shape, and minute structure. Thus, as has already been mentioned, the red blood-corpuscles contain no nucleus, but they do contain a pink compound, hæmoglobin, which endows these cells with the ability to carry oxygen. Muscle cells vary in shape and size according to the function they perform. If they are smooth muscle-fibres, as found, for example, round the lumen of the intestinal tract or blood-vessels, they are fusiform cells having a fine longitudinal striation. If, on the other hand, they come from a voluntary muscle they are larger, multi-nucleated cells, having a fine cross-striation. The cells lining the nose are provided with fine cilia which may perform active movement. Those from glands may be filled with granules containing the secretory material peculiar to those glands. Differences such as these enable us to differentiate between cells found in one part of the body and those found in another. Each tissue has its characteristic appearances whereby it may be recognised. When practised we can judge whether some of these structures were functionally active or were resting when they were taken for histological examination, and we can recognise in them the presence of abnormality produced by disease.

SECTION II

CHEMISTRY OF CELL CONTENTS.—If we analyse the protoplasm which the cell contains we find that it consists partly of organic and partly of inorganic substances. The organic substances can be subdivided in turn into those which contain nitrogen and those which do not. The latter are subdivided into carbohydrates, fats, and lipoids. The nitrogenous constituents of the cell are called proteins. They are classified under the following headings :—

(a) *Protamines*, simple basic proteins found in spermatozoa.

(b) *Histones*, also basic in character, *e.g.* globin, the protein part of the oxygen carrying pigment hæmoglobin.

(c) *Albumin*, found in most of the body fluids, forms colloidal solutions in water.

(d) *Globulin*, also found in most of the body fluids, is insoluble in water but is soluble in dilute salt solutions.

(e) *Phosphoproteins*, containing phosphorus, *e.g.* caseinogen is the principal protein of milk.

(f) The *scleroproteins*, from which the fibrous tissue, hair, nails, and other horny parts of the body are constructed. Many of these contain large quantities of sulphur.

(g) The *nucleoproteins* which are constant constituents of cell nuclei, and contain nucleic acid.

(h) *Glucoproteins* are proteins combined with a carbohydrate radical ; mucin is an example.

(i) *Chromoproteins* are proteins combined with a pigment. The best example is hæmoglobin, which is globin (see (b) above) combined with the iron-containing radical hæmatin.

(j) *Derived proteins*. These include acid metaprotein, formed from proteins during gastric digestion ; alkaline metaprotein, formed during intestinal digestion ; primary and secondary proteoses ; peptones and polypeptides, which are further stages in protein breakdown.

THE CONSTITUTION OF PROTEINS.—By hydrolysing proteins with dilute mineral acids or with the appropriate digestive ferment, their large molecules may be split into their constituent amino-acids. The proteins vary : (1) by the absence of one or more of these elementary amino-acids, (2) by containing different amounts of the amino-acids, (3) by the actual manner in which these various amino-acids are grouped together to form the large protein molecule.

Acid.	Amino-derivatives.
Acetic, CH_3COOH	Amino-acetic acid (glycine). Methyl-amino-acetic acid (sarcosine).
Propionic, $\text{C}_2\text{H}_5\text{COOH}$	Amino-propionic acid (alanine). Oxy-amino-propionic acid (oxy-alanine or serine). Phenyl-amino-propionic acid (phenyl-alanine). Oxy-phenyl-amino-propionic acid (tyrosine). Indole-amino-propionic acid (tryptophane). Iminazol-amino-propionic acid (histidine). Di-amino-thio-propionic acid (cystine).
Valerianic, $\text{C}_4\text{H}_9\text{COOH}$	Amino-valerianic acid. Guanidin-amino-valerianic acid (arginine).
Caproic, $\text{C}_5\text{H}_{11}\text{COOH}$	Amino-caproic acid (iso-leucine). Amino-isobutyl-acetic acid (leucine). Di-amino-caproic acid (lysine).

The following table shows the amino-acid constitution of some common proteins :—

	Serum-Albumin.	Egg-Albumin.	Caseinogen.	Gelatin.	Zein.	Gliadin.	Salmine.	Keratin.
Glycine . . .	0.0	0.0	0.0	25.5	0.0	0.9	0.0	4.7
Alanine . . .	2.7	8.1	1.5	8.7	9.79	2.7	..	1.5
Serine . . .	0.6	..	0.5	0.4	1.02	0.12	7.8	0.6
Phenyl-alanine . . .	3.1	4.4	3.2	1.4	6.55	2.6	..	0.0
Tyrosine . . .	2.1	1.1	4.5	0.01	3.55	2.4	..	3.2
Tryptophane . . .	present	present	1.9	0.0	0.0	1.0	..	present
Cystine . . .	2.3	0.2	..	0.0	..	0.45	..	over 10
Amino-valeric acid . . .	..	..	7.2	0.0	..	0.3	4.3	0.9
Leucine . . .	20.0	7.1	9.35	7.1	19.55	6.0	0.0	7.1
Lysine . . .	..	2.15	5.95	5.9	0.00	0.0	0.0	1.1
Arginine . . .	..	2.14	3.81	8.2	1.55	3.4	87.4	4.5
Histidine . . .	..	..	2.5	0.9	0.43	1.7	0.0	0.6
Proline . . .	1.0	2.25	8.0	9.5	9.04	2.4	11.0	3.4
Glutamic acid . . .	7.7	8.0	21.0	5.8	26.17	36.5	..	3.7
Aspartic acid . . .	3.1	1.5	4.1	3.4	1.71	1.3	..	0.3
β -hydroxy-glutamic acid . . .	..	..	10.0	0.0	..	..	..	..

It will be observed that some proteins are notable for a high content of one of the amino-acids. Thus: serum-albumin for leucine and cystine; egg-albumin for alanine and phenyl-alanine; caseinogen for tyrosine and amino-valeric acid; gelatin for

glycine; zein for leucine; gliadin for glutamic acid; salmine for arginine; and keratin for cystine.

On the other hand, some proteins have a very low content of certain of the amino-acids. This applies particularly to tryptophane, tyrosine and lysine, for these amino-acids are essential for growth in children and the maintenance of weight in adults. Histidine and cystine are also stated to be essential. It will be seen that gelatin and zein contain no tryptophane or cystine, and, in addition, the latter contains no lysine. The tyrosine content of gelatin is low; consequently neither zein nor gelatin alone form adequate protein foods.

This important aspect of nutrition will be referred to again in Chapter XVIII.

FATS.—The fats met with in the body are tristearin, $C_3H_5(C_{17}H_{35}COO)_3$, tripalmitin, $C_3H_5(C_{15}H_{31}COO)_3$, and triolein, $C_3H_5(C_{17}H_{33}COO)_3$. Three facts will be noticed about the above compounds. Each consists of a glycerol molecule, $C_3H_5(OH)_3$, the three OH groups of which have been replaced by fatty acid radicals; secondly, that the acid radicals in tristearin and tripalmitin are part of the same series, stearic acid being of a higher order than the palmitic acid. Thirdly, it will be observed that triolein contains an acid radical in which two hydrogen molecules are missing from one stearin molecule. In consequence triolein itself and the fatty acid which it contains are called unsaturated. They combine very easily with such substances as iodine, which takes the place of the missing hydrogen molecule. Fats insoluble in water become soluble when combined with alkali to form soaps.

LIPIDS.—These substances are found in the protoplasm of cells. They form important constituents of the cell envelope, and have many physical properties which resemble those of the fats. They are insoluble in water, but freely soluble in most organic solvents. In consequence of this, organic materials and, incidentally, gases, can generally pass easily through the cell wall into the protoplasm inside, while water-soluble inorganic constituents cannot as a rule do so except in very small quantities. Two lipoids should be specially mentioned, lecithin and cholesterol. Together they form the envelope of the red blood-corpuscle, while cholesterol ($C_{27}H_{45}OH$) is a constituent of the bile, and is related to ergosterol, which under the action of light is transformed into a potent substance which prevents rickets. It will be seen in Chapter XVIII that vitamin D has a similar property. The substance produced by the action of the light may be identical with this vitamin.

CARBOHYDRATES.—The carbohydrates contain twice as many hydrogen atoms as oxygen atoms in their molecule. Glucose, $C_6H_{12}O_6$, is commonly found in the body. It is the form in which carbohydrate is conveyed from one part of the body to another. For example, carbohydrate foods absorbed from the digestive tract, travel through the blood to the liver as glucose, or, if the muscles require carbohydrate, it is as glucose that it passes through the blood from the liver. In milk, carbohydrate appears in the form of the di-saccharide lactose. This has the formula $C_{12}H_{22}O_{11}$. After hydrolysis by acid or enzyme this di-saccharide is split into one molecule of glucose which, being dextro-rotatory to polarised light, is frequently called dextrose, and one molecule of galactose, which is also dextro-rotatory. In addition, we find in food two other di-saccharides: (a) cane-sugar, also called sucrose, which after hydrolysis is split into one molecule of glucose and one molecule of fructose which, being lævo-rotatory, is also called lævulose; and (b) maltose which, on hydrolysis, forms two molecules of glucose. Lastly, there are the poly-saccharides, the most important of which are starch, found in vegetables, and glycogen, found in the body, *e.g.* in the liver and the muscles. These poly-saccharides have the general formula $(C_6H_{10}O_5)_n$. They may be distinguished by the colours they produce with iodine: blue for starch, but port-wine colour for glycogen. Another poly-saccharide, cellulose, forms the cell wall of most plant cells. The animal digestive enzymes have little effect on it, and, except for the action of bacteria, it passes through the digestive tract unchanged.

COLLOIDS.—The term colloid was originally applied to all substances, such as starch and proteins, which would not form crystals or pass through an animal membrane, in contradistinction to easily crystallisable bodies, such as sugar, which diffuse rapidly through animal membranes and are called crystalloids.

It is now known that the colloidal state is a condition of suspension of particles which are too small to sediment and which exhibits certain characteristic features, and that a very large number of substances, including metals, may exist in the colloidal form.

Most colloids consist of very small particles or very large molecules or aggregates of molecules, and their characteristics depend largely on the fact that they do not form true solutions in water or other solvents, but that their pseudo-solutions consist of particles in suspension. Owing to the size of the particles, colloidal suspensions do not follow the laws of true solution, *e.g.* they exert only a very small osmotic pressure, they exhibit

some degree of turbidity, or power of scattering light when a strong beam of light is passed through them, and they have a high viscosity compared with water.

Most of the colloids which are of importance in physiology are suspensions of liquid particles, *i.e.* they are fine emulsions, and are called *emulsoid* colloids to distinguish them from fine solid suspensions, which are known as *suspensoid* colloids. The suspended particles in nearly all colloidal solutions are electrically charged, but often the charge can be altered. Thus, globulins or albumins in acid solutions have positively charged particles, and in alkaline solutions negatively charged particles.

If an electrolyte, such as sodium chloride, is added to a colloidal suspension, the salt concentrates at the surface of each colloidal particle, this process being called *adsorption*. Its occurrence can be readily demonstrated by dipping strips of blotting paper, which is colloidal, into a solution of a dye. The dye accumulates on the particles in the paper, and the latter becomes more deeply coloured than the solution into which it is dipped.

The amount of adsorption is relatively much greater in dilute than in strong solutions of the electrolyte. Its importance lies in the fact that the velocity with which a chemical change takes place varies with the concentration of the interacting substances. If two electrolytes, which can interact, are added to a colloidal solution, they become concentrated on the surface of the colloidal particles, and at these surfaces the reaction between them will therefore proceed more rapidly than if the colloid were absent.

Solutions of colloids are called *sols*; in certain circumstances the particles may aggregate into larger masses, forming a precipitate, or the solution may change to a jelly, called a *gel*. An example of this process is the coagulation of protein by heat.

Some colloids, such as hæmoglobin, are crystallisable.

SECTION III

THE PHYSIOLOGY OF THE CELL MEMBRANE.—In this section cell membrane is defined as the boundary layer that separates the cell protoplasm from some other medium which differs from it in chemical composition. It not only includes, therefore, the outer boundary layer of the cell, but also the internal boundaries, *e.g.* round vacuoles or particles which the cell has itself secreted.

If we look at the normal function of living cells we see that it is to convert one kind of energy into another. If we try to classify such manifestations of energy we find that they can be subdivided into the following groups. The cell may receive the

energy supplied to it in the form of food materials and oxygen, and may convert them into: (a) mechanical energy; (b) electrical energy; (c) light energy; (d) chemical energy; (e) stored energy. Let us examine some of these in detail.

The mechanical energy may be devoted to moving the cell itself, as in the amoeboid movements of the white corpuscles of the blood, or in moving something else, as in the various muscles. Electrical energy—that, for example, which accompanies muscular contraction or the conduction of the nerve impulse—is a form of energy which is specialised in the electric organ of certain fish. Light energy is evolved by a number of insects. Careful examination shows that this may be produced in two ways: either the cell itself produces light, or it produces a substance from which light may subsequently be obtained by some further chemical process. In the same way, chemical energy may be shown locally by the cell itself, or it may prepare a substance which is able to effect interchanges of chemical energy, *e.g.* the enzymes. Lastly, stored energy. Not only have we the example of fats laid down in adipose tissue or of glycogen stored in the liver, but we have the case of oxygen storage which is effected by the compound hæmoglobin, contained in the red blood-corpuscles. If we critically examine all these different manifestations we find, so far as we know without exception, that cell membranes are involved, and the reactions which take place across such cell membranes are, therefore, of considerable interest. Firstly, there is the development of osmotic pressure, which will be considered in a later section of this chapter, and secondly, there is the phenomenon of surface tension which we find exhibited by the soap bubble and by the rise of fluid in the capillary tube.

SECTION IV

REPRODUCTION OF CELLS.—Important as are the changes of energy which have been enumerated in the last section, they take second place to the extraordinary power of living cells to reproduce themselves. I do not refer only to that very special kind of reproduction which results in the formation of an embryo, but also to that infinitely more common type of reproduction by which tissue growth or tissue repair is effected. Thus, in normal tissues, when cells die from old age or hard usage, their place is taken by new cells which have been produced by the division of other older cells similar, in all other respects, to themselves.

This division may be of two types, amitotic and mitotic. Amitotic division is a very simple process, but, so far as is known, it rarely takes place in human tissues. The nucleus, initially

spherical, is seen to slowly develop an hourglass-like constriction. The waist joining the two larger portions gradually narrows until separation has been effected. The two halves of the nucleus then separate from one another until the cell body begins in its turn to develop an hourglass-like constriction. This is followed by a division of the body into two halves and the amitotic division is complete.

Mitotic division is far commoner and far more complicated than that just described.

The attraction sphere with its astral rays separates into two. As these draw apart, streaks are still seen joining them through the cell substance, the achromatic spindle. The chromatin of the nucleus forms a long continuous skein, then this skein separates into short lengths, the number of which is characteristic of the animal to which the cell belongs. In the case of human beings the number is forty-eight. The outer membrane of the nucleus disappears and these short lengths of chromatin arrange themselves in star formation. This star lies midway between the two attraction spheres. Each short length now divides longitudinally into two and each half travels towards the attraction sphere which is drawing it. In consequence forty-eight half-pieces cluster round one attraction sphere and forty-eight round the other. These now form continuous skeins, a nuclear membrane forms round the outside, the skeins break up into little pieces of chromatin, the two nuclei have the same appearance as the original nucleus from which they were formed, except that they are smaller. The separation of the cell bodies now follows, beginning with an hourglass-like constriction, and is rapidly completed by the separation of the two halves, as in amitotic division. Observation of the growing tip of an onion or a rapidly growing embryo will readily demonstrate cells which have been fixed in all stages of mitotic division. The time taken by this whole process varies from half-an-hour to three hours. Further details will be found in Chapter XXIII.

SECTION V

FACTORS ESSENTIAL TO LIFE.—It will be shown in the following sections that there are a number of conditions which must be met with in the environment of the cells in order that life may persist.

(1) The osmotic pressure of the electrolytes present in the solution which is in contact with the cells must have the correct value.

(2) Certain specific electrolytes must be present in certain specific quantities.

(3) The concentration of H ions and OH ions must lie between narrow limits.

(4) Certain inorganic constituents must be present.

(5) The temperature must lie between certain narrow limits.

(6) There must be a means of obtaining oxygen and of getting rid of CO_2 and other breakdown products.

(7) There must be an adequate diet.

(1) **IMPORTANCE OF OSMOTIC PRESSURE.** — Osmotic pressure is developed by substances in solution. It is measured by an osmometer (see Fig. 1). If, having taken some ordinary

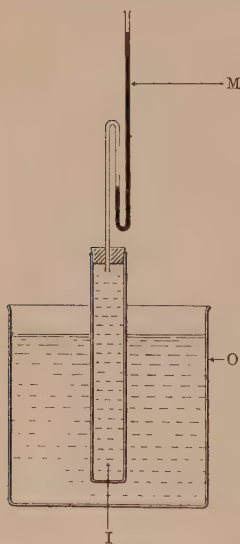


FIG. 1.—The osmometer.

O = Outer vessel containing distilled water.

I = Inner semi-permeable vessel containing sodium chloride solution.

M = Mercury manometer for recording the osmotic pressure.

some of the weaker ones cause what is called a laking of the blood. That is, the opaque appearance of normal blood disappears, and a transparent solution is formed. If we examined under a microscope the events which were occurring, we should see that the red blood-cells were swelling up owing to the passage of water into them. A stage would soon be reached when their outer envelope could no longer withstand the internal pressure and, in consequence, the red blood-corpuscles would rupture, their intracellular content passing into solution. If we made similar microscopic examination of cells which had been in contact with the other NaCl solutions, and if we compared the cells that we saw there with those of normal undiluted blood, we should see that the red blood-cells in the NaCl solution of approximately 0.95 to 0.85 per cent. are of approximately normal appearance. Those in NaCl solutions less concentrated than this, would have cells larger than the normal,

although the swelling might not have been sufficient to bring about laking. On the other hand, the red blood-corpuscles in solutions having a greater concentration than the 0.95 to 0.85 per cent. would be seen to be smaller than normal cells, their outside envelope being wrinkled and their internal content shrivelled.

The explanation of this phenomenon is that the osmotic pressure of the material inside the red cells is about the same as that of the 0.95 to 0.85 per cent. NaCl solution. When

the cells are immersed in a solution which has the same osmotic pressure as themselves, water does not tend to pass from one into the other because the competition for water is the same in both cases. On the other hand, if the red cells are immersed in a fluid which has a lower NaCl concentration, the higher osmotic pressure of the cell content causes the water to flow through the cell membrane from the weaker NaCl solution outside. This process continues until the salts inside the cell have become so diluted that their osmotic pressure is approximately equal to that of their surroundings. Alternatively, if the NaCl concentration outside the cells exceeds that inside them, the greater osmotic pressure of the surrounding liquid causes water to flow through the cell membrane from the interior of the cells into their surroundings. The cell content in consequence shrivels. This process goes on until so much water has left the cells that the concentration of salts inside them has become equal to the concentration of salt outside them, and the process then stops.

Red blood-cells are typical of practically all the cells of the body in the exhibition of these phenomena. Very serious damage to cells results if distilled water or ordinary tap water be injected into a large vein. The red blood-corpuscles swell up and burst, and the same thing would happen in the tissues of the body if distilled water were injected there. On the other hand, if strong NaCl solution were injected a shrivelling of the cells would take place, and for the time being they would cease to carry out their normal functions and might be killed.

If we drink large quantities of water, this water passes slowly, a little at a time, through the lining membrane of our digestive tract into our blood and almost at once the kidneys commence to secrete into the ureters a urine which has an NaCl concentration below the normal, and this elimination of a nearly salt-free fluid continues until the osmotic pressure of the blood has been returned to the normal. Alternatively, if we drink a very strong salt solution we promptly vomit. If by trial we obtain an NaCl solution which can be tolerated, then we find that this passes, a little at a time, through the wall and digestive tract into the blood and, as a result, very shortly afterwards the kidneys commence to secrete a urine which has a salt concentration far above the normal. In addition, we probably experience a sensation of profound thirst, which usually drives us to consume large quantities of water, thus assisting in the restoration of the normal osmotic pressure of the blood.

(2) **IMPORTANCE OF SALT BALANCE.**—In addition to the requirement that the osmotic pressure of the fluid surrounding

the cells shall have a correct value, we find that the separate concentrations of the electrolytes bathing the cells must be of the right value. Suppose, for example, that having removed the heart from a frog, we perfused it with an NaCl solution having a concentration of 0·75 per cent., we should find that the heart came to a standstill in a comparatively short time. If now we prepared solutions of potassium chloride and calcium chloride, all of the same osmotic pressure as that of the sodium chloride, we should find that additions of small amounts of calcium and potassium increased the length of time during which the heart can beat. If we performed a sufficient number of tests we should find that there were favourable concentrations for each of these salts. If we now compare these latter concentrations with those of the same salts inside the plasma (that is the fluid part of the blood) of the frog, we should find that the concentrations were identical. We should improve our results still more if we added a small quantity of alkali to prevent the solution from becoming acid, and if we shook it vigorously with air so that it took up O_2 in solution; also if we put in it small quantities of glucose and added small quantities of various other substances. In other words, the more nearly our artificial solution corresponded in its chemical composition with the chemical composition of plasma the better would our results be, and the longer would the heart survive. The fluids associated with the names of Ringer and Locke have originated by experiments performed on these lines.

(3) IMPORTANCE OF H ION AND OH ION CONCENTRATION.—The H ion concentration is the number of gramme equivalents of ionised hydrogen in a certain number of litres of water. Thus, if we say the H ion concentration is $\frac{1}{10 \text{ millions}}$ we mean that 10 million litres of water contain 1 gramme of ionised hydrogen. It must be understood at the outset that the H ion and OH ion concentrations are inter-related with one another as the following table will show :—

Concentration of H ions	Concentration of OH ions
$\frac{1}{10 \text{ millions}}$	$\frac{1}{10 \text{ millions}}$
$\frac{1}{1 \text{ million}}$	$\frac{1}{100 \text{ millions}}$
$\frac{1}{100 \text{ millions}}$	$\frac{1}{1 \text{ million}}$
$\frac{1}{1000 \text{ millions}}$	$\frac{1}{100,000}$

It will be seen that if $\frac{1}{x}$ is equal to the concentration of H ions, and $\frac{1}{y}$ is equal to the concentration of OH ions, $x \times y$ is always 100 million millions. Thus, for example, if $x = 2$ millions, then $y = 50$ millions, and therefore if the H ion concentration is $\frac{1}{2}$ millions then

the OH ion concentration is $\frac{1}{50}$ millions. If we know the value of one we also know the value of the other (or can easily find it out by means of the above table).

Now the H ion concentration is frequently stated on what is known as the P_H scale. When the H ion concentration is $\frac{1}{10}$ millions the P_H of the solution is 7. If it be 10 times stronger

than this, namely $\frac{1}{1}$ million, it is clearly more acid and the P_H is 6. P_H 8 will correspond to an alkaline solution because

the concentration of H ions is $\frac{1}{100}$ millions, whereas the con-

centration of OH ions as we have seen from the above table is $\frac{1}{1}$ million, *i.e.* 100 times as strong. We see in each case that the

P_H number states the number of noughts in the fraction expressing the concentration of H ions and the P_{OH} is correspondingly the number of noughts in the fraction expressing the hydroxyl ion concentration. We can therefore construct the following table:—

Concentration of H ions	P_H scale
$\frac{1}{1}$	P_H 0
$\frac{1}{10}$	P_H 1
$\frac{1}{100}$	P_H 2
$\frac{1}{1000}$	P_H 3
$\frac{1}{10,000}$	P_H 4
$\frac{1}{100,000}$	P_H 5
$\frac{1}{1}$ million	P_H 6

Concentration of H ions	P_H scale
$\frac{1}{10 \text{ millions}}$	$P_H 7$
$\frac{1}{100 \text{ millions}}$	$P_H 8$
$\frac{1}{1000 \text{ millions}}$	$P_H 9$
$\frac{1}{10,000 \text{ millions}}$	$P_H 10$
$\frac{1}{100,000 \text{ millions}}$	$P_H 11$
$\frac{1}{\text{million millions}}$	$P_H 12$
$\frac{1}{10 \text{ million millions}}$	$P_H 13$
$\frac{1}{100 \text{ million millions}}$	$P_H 14$

To find the OH ion concentration on the P_{OH} scale all one need do is to subtract the P_H number from 14. For example, what is the P_{OH} when the P_H is 3? Since $14 - 3 = 11$, the $P_{OH} = 11$. The concentration of OH ions will be expressed by a fraction with eleven noughts, that is, it will be $\frac{1}{100,000 \text{ millions}}$. Now when

the figures for P_H and P_{OH} are the same, the concentrations are the same. In other words, the solution is neutral. It is obvious that this happens when $P_H = 7$, since then P_{OH} also equals 7.

Now normal blood has a P_H of approximately 7.4, which means that it is definitely on the alkaline side of the neutral point. Experiments on animals show that a more alkaline P_H , even up to $P_H 9$, can be tolerated by the tissues of the body and not cause death, particularly if the alkalinity persists for a short time only. On the other hand, similar experiments show that the P_H of the blood cannot go far on the acid side of the normal reaction without harm; that is, not much below $P_H 7.25$. It will be noticed that the change is much smaller than that which can be tolerated on the alkaline side. It will also be observed that this $P_H 7.25$ is still on the alkaline side of the neutral point. The P_H of the blood is adjusted under normal circumstances by two important mechanisms: (1) the respiration, and (2) excretion by the kidney.

THE BUFFER SALTS IN THE BLOOD.—In addition to the salts that we have already considered, namely, the chlorides of

sodium, potassium, calcium, etc., there are two important compounds, the bicarbonates and the phosphates. The importance of these lies in the fact that they behave in the blood as "buffers." The explanation of their mode of action is as follows: If we took three test tubes, one containing distilled water, the next a 1 per cent. solution of sodium bicarbonate, and the third a 1 per cent. solution of alkaline sodium phosphate (Na_2HPO_4), and if to each of these we added 1 c.c. of a dilute mineral acid such as HCl , we should find that the distilled water would undergo a very big change of P_{H} , in other words, would become strongly acid. Such, however, would not be the case with the solutions in the other two tubes. There would have been a change towards the acid side, but it would have been quite a small one. Suppose now the contents of these tubes are very thoroughly shaken with air, the contents of the third tube would probably be found to have the same P_{H} as before. That of the second tube, however, would probably have lost some of its acidity. Two things are clear, then: first that both sodium bicarbonate and sodium phosphate act as "buffers," and also that if air is allowed to come into intimate contact with both then the sodium bicarbonate is the more effective buffer. The mode of action of these buffers may now be briefly considered.

On adding to distilled water a small quantity of a common mineral acid, free dissociation of the acid takes place, in consequence of which enormous numbers of free hydrogen ions are present, causing the solution to have a strongly acid reaction. In a solution containing sodium bicarbonate, where the dissociation is quite weak, there are a few free sodions and a few free acidions. Of the two in the present case the sodions are more powerfully basic than the HCO_3 ions are acidic, and in consequence the solution is faintly alkaline. Suppose we add to this solution a few c.c. of a dilute mineral acid, for example, HCl . The following reaction takes place:—



We have produced sodium chloride and carbonic acid. Now the sodium chloride dissociates and the products of its dissociation are neutral. The carbonic acid dissociates but little and its products are weakly acid. The final solution, therefore, has a slightly acid reaction. On shaking with air, however, a great part of the carbonic acid disappears, carbon dioxide gas passing into the air, the water with which it had temporarily combined remaining behind. The slight acidity of the solution due to the carbonic acid is thus removed. We can explain therefore not only the powerful buffering action of the sodium

bicarbonate solution, but also the improvement in buffering if that solution is allowed to have free access to the air. In the case of alkaline sodium phosphate the reaction would be as follows :—



We see that the addition of mineral acid causes the formation of sodium chloride, which is neutral, and the replacement of alkaline sodium phosphate by acid sodium phosphate. These two salts of phosphoric acid when in solution have different P_H values, as their names suggest. But the change in P_H is much less than it would have been if the same quantity of HCl had been added to distilled water only. We shall see later that there are two other highly important ways in which the blood is buffered: (1) by the proteins of the blood, and (2) by the corpuscles. Suppose, therefore, that a dilute solution of a mineral acid were cautiously injected into the blood of an animal: there would be an immediate reaction between the acid and the buffer substances which the blood contains. Let us focus our attention on the sodium bicarbonate. We have already seen that the products are sodium chloride and carbonic acid. The latter acts as a powerful stimulant to the respiratory centre, greatly increasing the ventilation of the lungs. The animal would, therefore, greatly increase its respiratory efforts, in consequence of which the blood circulating through the lungs would be brought into very intimate contact with the air which repeatedly fills the lungs. Carbonic acid would disappear from the blood and carbon dioxide gas would be found in the air leaving the lungs. This process would continue until a normal state of affairs had been resumed. The respiratory organs having done their share of the work, it remains for the kidney to perform its part, which consists of the elimination of the NaCl. This is effected usually within three or four hours of the injection. Tests on the reaction of the blood would show that it had returned to its normal P_H .

If the amount of acid injected was large it would be found that the urine became more acid than normal, and there would be found in it considerable quantities of ammonia combined with the injected acid to form a salt. Under normal circumstances practically all this ammonia is excreted as urea. It comes from the amino groups of those proteins which are not required for bodily repair. This is the third way in which acids may be eliminated. This important subject will be dealt with in detail in Chapter XXI.

Suppose, on the contrary, that a dilute solution of alkali had been injected into the animal's blood. The respiratory efforts

would be reduced below the normal and tests made on the expired air would show that there is less CO_2 being excreted than would be found under normal circumstances. The following equation shows what would be happening if sodium hydroxide had been the alkali administered :—



The accumulated CO_2 forming carbonic acid in solution would react with the soda, producing sodium bicarbonate and water. The sodium bicarbonate, if in excess of the bodily requirements, would be subsequently excreted by the kidney, probably as some other sodium compound, the CO_2 being excreted by the lungs in the usual manner.

(4) IMPORTANCE OF INDIVIDUAL INORGANIC CONSTITUENTS.—There are two further important aspects of the salts which must be mentioned: (1) the part they play in forming some of the bodily constituents, and (2) the part they perform in some of its reactions. For example, calcium, which is taken in with vegetables, milk, and meat, is essential for the formation of bone, the hardness of which is due to calcium phosphate. In addition, the clotting of milk in the stomach, the coagulation of blood at injured surfaces, and the activation of the important digestive ferment trypsinogen are all dependent on the presence of calcium ions. Moreover, the normal activities of the heart, capillaries, nerves, and muscles depend on calcium salts being present in the fluid which bathes them. Further examples will be met with in subsequent chapters, showing the important specific effects of other inorganic constituents. It is, therefore, clearly essential that an adequate diet should contain them.

(5) IMPORTANCE OF TEMPERATURE.—We may roughly divide living matter into three groups :—

Group I, containing the bacteria and other primitive living organisms. This group will stand, for a short time at all events, the application of quite extreme degrees of heat and cold. Dry bacteria can be heated to the temperature of boiling water and can be cooled far below the freezing point of water and will show afterwards normal activity and growth. Their spores are frequently even more resistant than themselves. Even plant seeds can withstand quite big temperature variations from the normal.

Group II, containing the cold-blooded animals, such as frogs,

reptiles, and fish. This group cannot stand the same temperature variations as can Group I. If they are taken to a temperature above 40° C. or much below the freezing point of water, they perish.

Group III, which includes warm-blooded animals, mammals, birds, and the like. This group can withstand somewhat larger temperature variations than can Group II, but only because they are able to control the internal temperatures of their bodies, in which it is found that relatively small variations of temperature occur. If, as the result of disease or experimental interference, the body temperature is much changed from its normal value, serious consequences follow. For example, a raising of the blood temperature from about 41° C. causes heat-stroke and death. When subjected to extreme cold the blood temperature may fall to nearly 20° C.; the individual becomes comatose before such a temperature is reached and will quickly die if some external agent is not applied to raise the body temperature. From this point of view we see, therefore, that the cells which make up the individuals of Group III are able to withstand smaller temperature variations from the normal than can those of Groups I and II.

In normal circumstances the variations in temperature which the body undergoes are quite small; it is common knowledge that it remains at approximately 37° C. (98·4° F.) under widely varying conditions. Even severe muscular exercise, which involves a very big liberation of heat in the body, raises it only some 3° C. (5° to 6° F.). When we are feeling extremely cold our body temperature is seldom more than 1° C. below the normal. The way that the temperature of the body is regulated will be considered in detail in Chapter XIX.

(6) THE IMPORTANCE OF OXYGEN INTAKE AND CO₂ OUTPUT.—Oxygen is a universal requirement of living animal matter. It is required for the combustion of chemical compounds containing carbon, the object being that the energy thus liberated shall be available for the energy requirements of the animal. Thus, the carbohydrate glucose which has the formula C₆H₁₂O₆ requires 6 molecules of oxygen for its combustion, the result being that 6 molecules of CO₂ are produced, as is shown by the following equation:—



Every gramme of carbohydrate thus oxidised provides about 4·1 large Calories of heat. Since an adult man at rest requires approximately 2500 large Calories of energy per day, this means that he must oxidise roughly 600 grammes of carbohydrate or some other equivalent substances daily. For this he will require

640 grammes of oxygen, that is, 450 litres in the 24 hours, which works out at nearly 315 c.c. per minute. Now the amount of oxygen in inspired air is 21 per cent., and that in expired air 16 per cent., which means that 5 per cent. of the inspired air is absorbed by the lungs as oxygen. In order that 315 c.c. of oxygen should be provided, 6300 c.c. of air must have passed into and come out of the lungs per minute. If the man takes sixteen breaths per minute each breath will deal with approximately 400 c.c. This emphasises the importance of the respiratory function so far as the intake of oxygen is concerned. With regard to the carbon dioxide, it will be seen that the same volume of CO_2 has to be excreted as that of the oxygen which is absorbed, since the ratio of CO_2 excreted to oxygen absorbed, which is known as the *respiratory quotient*, is 1 in the case of carbohydrate.

(7) **THE IMPORTANCE OF CORRECT DIET.**—The objects of diet are to make good all the deficiencies which have occurred in the body as a result of its activity. We have already seen that carbohydrate is required in order to produce energy. Some of this may be replaced by fats. These latter are rich in carbon and hydrogen but have less oxygen than the carbohydrates. They produce a greater yield of heat on oxidation : 1 gramme of fat produces on the average 9.3 large Calories of heat, that is, rather more than double the amount yielded by 1 gramme of carbohydrate. Fats are, therefore, comparatively concentrated sources of heat. It is not possible, however, to replace the whole of the carbohydrate by them without causing digestive disturbances. Lastly, the proteins may be used as sources of energy. They yield about the same number of Calories per gramme as carbohydrates do, and the replacement of carbohydrate by protein has no disadvantages other than that of cost. Foods rich in protein, *e.g.* lean meat, are invariably more costly than foods rich in carbohydrate, *e.g.* wheat or potatoes.

In addition to providing the necessary number of heat units in the diet, it is essential that the protein breakdown of the body should be made good. The performance of muscular work involves the disintegration of a certain weight of muscle protein. This has to be replaced by proteins in the diet. Now, as will be shown later, it is not sufficient that 1 gramme of protein should be taken in for each gramme of body protein disintegrated, because not only is it essential to make good the protein disintegration as a whole, but it is essential to make good the waste which has occurred in each of the separate proteins of which the body is composed. Whereas, theoretically, about 50 grammes of protein would be satisfactory if the proteins were interchangeable,

we find that as they are not, the protein requirement is approximately 80 to 100 grammes per diem. This important subject will be referred to in greater detail in Chapter XVIII, on Diet.

We have, further, to provide water, salts, and vitamins. With regard to water we may say that the minimum quantity is about 1 litre per diem. The majority of people drink considerably more than this, perhaps 2 or 3 litres, and in summer the amount may be largely increased. This fluid is got rid of by three principal routes: (a) by the kidney; (b) by the sweat glands; and (c) by the lungs. The latter is relatively unimportant. Now it is essential that waste products should be eliminated and these, so far as the kidney of man is concerned, have to be in solution. The average man excretes approximately $1\frac{1}{2}$ litres of urine per day, but this may be reduced with a corresponding increase in concentration of the urinary constituents. The amount excreted by the sweat-glands varies greatly according to the external temperature. In cold weather the amount of fluid evaporated by the skin may be extremely small. If water largely in excess of that ordinarily consumed is taken voluntarily by a man, or is administered experimentally to animals, there is vomiting and periods of convulsions alternating with coma. Post-mortem examination shows but little. Œdema of some of the tissues is found and this may involve the contents of the cranial cavity. Alternatively, if fluid is withheld the symptoms of thirst very quickly manifest themselves. There is a feeling of dryness in the throat and mouth; the conjunctivæ sting; the lips commence to crack; speech begins to be difficult because of the dryness of the mucous surfaces involved; the skin becomes dry and hard; there is severe discomfort; mental disturbance is very great; the secretion of urine ceases; after a time the individual becomes comatose and dies, very probably as the result of poisoning by accumulation of his own metabolic products. A man can do without food for many days without serious discomfort and without risk of life. Periods as long as a month have been successfully withstood. On the contrary, deprivation of fluid very rapidly produces discomfort and death ensues in a comparatively short time.

The necessity for inorganic salts has already been emphasised in Sections (1), (2), and (3) above. They are usually obtained in sufficient amount in the food and liquid which the individual consumes. In addition, salt, which is usually an impure sodium chloride, potassium and calcium chlorides also being present, is frequently added as a condiment.

Lastly, it is essential that the food should contain vitamins.

The importance of these substances has been emphasised to an increasing extent as the result of recent research work. Six of them are known at the present time, and the existence of more of them is suspected. Their effects on the well-being of the body, on its growth, on its ability to reproduce itself and to ward off the attacks of bacteria, are becoming increasingly apparent. This important aspect of diet will be found referred to in detail in Chapter XVIII.

SECTION VI

TISSUE CULTURE.—If the conditions necessary for life are complied with, experiment shows that not only may such tissues as muscle and gland be made to “live” for a time after their removal from the body but also that the tissues may be made to “grow.”

Certain conditions must be observed in carrying out experiments on such surviving tissues, *e.g.* oxygen must be supplied, and the chemical surroundings and temperature of the tissue must closely resemble those which the cells have in their natural state. The excised tissues are therefore usually suspended in a saline fluid similar in composition to the blood-plasma, or sometimes actual blood-plasma is employed.

If very small fragments of tissue are removed under aseptic precautions from young animals, and placed in warm sterile oxygenated blood-plasma, the growth of the tissues continues by rapid cell-division until a certain sized mass results. If a fragment of this mass be then transferred to fresh plasma, its growth is renewed; the process may be indefinitely repeated. This technique, known as *tissue culture*, illustrates the capacity of surviving tissues to continue their isolated existence and to grow even under somewhat abnormal conditions.

CHAPTER 11

MUSCLE

SECTION I

THREE varieties of muscle are found in the body : striated, unstriated, and cardiac. The striated muscles attached to the skeleton are sometimes called voluntary and are therefore referred to as voluntary muscles. The unstriated muscles are found in the walls of blood-vessels, the intestinal tract, the reproductive system, and elsewhere. Their contraction is independent of the will and they are therefore known as involuntary muscles. Cardiac muscle, as its name implies, forms the musculature of the heart.

HISTOLOGY OF STRIATED MUSCLE.—The fibres are cylindrical in shape, about 40 mm. long, and about one-tenth of a millimetre in diameter. Each has a structureless cell wall called the sarcolemma, and each possesses several oval nuclei, which lie close to the sarcolemma. Each shows a fine regular transverse striation which consists of alternate dark and light bands. Each light band is divided longitudinally into two equal parts by a line named after Dobie. Each dark band is similarly divided by a line of Hensen. The muscle is thus divided into a number of sarcous elements, each extending from one Dobie's line to the next, and

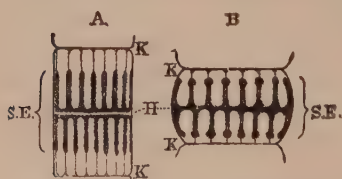


FIG. 2.—Diagram of a sarcous element, A, in a moderately extended condition; B, in a contracted condition; K, K, lines of Dobie; H, line of Hensen. (From Quain's *Anatomy*, by permission of Sir Edward Sharpey Schafer.)

consisting from one side to the other of half a light band, then a whole dark band, lastly another half light band. (See Fig. 2.) Under polarised light it will be seen that the lightness and darkness of the bands are reversed; the bands which were dark under ordinary light are now light; this indicates that the material of which they are formed has a solid structure and that it is under tension. On the contrary, the parts which were

light bands under ordinary light are now dark, indicating that the material of which they are made is not under tension, or is liquid, or both. If the contraction of a fibre be carefully watched under polarised light, it will be seen that the dark material seems to disappear into the light and that the light material swells. (See Fig. 3.) To the fluid which is dark under polarised light is given the name *sarcoplasm*. Very careful examination under high magnifications shows that the structure of the light material is that of enormous numbers of fine tubes whose long axes are parallel with the long axis of the muscle-fibre. When a muscle contracts the sarcoplasm appears to run into these fine tubes, causing them to increase in bore, and in consequence the dark band tends to disappear into the light band. Each sarcoelement when contraction is complete has therefore half the width that it had when completely relaxed. Its volume, however, remains the same as it was at first, and, therefore, at the same time that it shortens, its area correspondingly increases.

In certain animals such as the rabbit, some of the muscles are pale and others are red in colour. The pale muscles have the structure just described, whereas the red muscle-fibres contain more sarcoplasm than the pale ones, and their nuclei are scattered throughout the substance of the fibres. In many animals these two varieties of fibre are found together in the same muscle.

MOTOR END-ORGANS.—Muscles are supplied by two entirely separate kinds of nerves: motor nerves which cause them to contract, and sensory nerves which inform higher centres of the central nervous system of the degree of tension in the muscle and the amount of contraction which it has performed. The sensory and motor nerves are not unlike one another, but their terminations in the muscle are extremely unlike, and can be easily differentiated from one another. The endings of the motor nerves are called *motor end-organs*, those of the sensory nerves are called *muscle spindles*, and will be described in detail in Chapter X.

The motor end-organ consists of a flat disc of undifferentiated protoplasm which is applied to one side of the muscle-fibre lying



FIG. 3.—Photomicrograph by polarised light of a contraction wave travelling down a striated muscle. Note the disappearance of the dark material on contraction and the increased width of the fibre. (From Schaffer's *Essentials of Histology*.)

immediately underneath the sarcolemma. Into this protoplasm ramify the finely separated terminations of the motor nerve which has lost its medullary sheath as it enters the sarcolemma. It will be shown later that this undifferentiated protoplasm has certain particular chemical and physiological properties of its own.

CHEMISTRY OF STRIATED MUSCLE.—Muscle contains roughly 75 per cent. water and 25 per cent. of solid substances, proteins forming approximately 20 per cent. Muscle plasma contains about 4 per cent. paramyosinogen and about 16 per cent. myosinogen. Both these substances are globulins; the former undergoes heat coagulation at about 48° C., the latter at about 58° C. When solutions containing these substances are mixed, clotting takes place. This can be prevented by the removal of calcium salts.

In addition, muscle contains small quantities of fat and glycogen and a number of nitrogenous organic compounds, *e.g.* creatine, carnosine, xanthine, and hypoxanthine. Creatine, which forms roughly 0.4 per cent. of the muscle, is present in combination with phosphoric acid as phosphagen. Inorganic salts are also present in muscle.

THE CONTRACTION OF VOLUNTARY MUSCLE.—When a muscle is suitably stimulated, it undergoes a considerable increase in tension. This may be followed or not according to external conditions in an actual shortening of the muscle. In either case its increase in tension is referred to as a muscular contraction. In the intact animal, muscular contraction is initiated by a nerve impulse, but under experimental conditions other methods of stimulation can be shown to be effective, *e.g.* mechanical, chemical, or electrical stimulation. Thus, pinching a muscle or dropping small weights on it will initiate a contraction. Sodium chloride and guanidine both set up spontaneous contractions. The passage of a constant current through a muscle excites contraction, so also does the making or breaking of such a current, or a sudden variation in its strength. Alternatively, these different methods of stimulation may be proved to be effective when applied to the motor nerve going to a muscle. That suitable stimuli applied to muscle cause it to contract without the intervention of the nerve-fibres which ramify amongst its substance is shown by the fact that muscle which has had its nerve end-organs paralysed by curare will still respond to direct stimulation.

SECTION II

RECORDS OF MUSCULAR CONTRACTION.—When a muscle contracts it becomes shorter and thicker but undergoes no change in volume. The simplest way of recording the shortening is to attach one end of the muscle to some fixed object and to attach the other end of the muscle to a lever, the long end of which carries a writing point which can trace a record on a smoked revolving drum. When, as the result of stimulation, the muscle is caused to produce a single contraction, a record is obtained similar to Fig. 4. The tracing shows three phenomena: (1) the existence of a latent period between the time of stimulation, which is marked *St.* on the tracing, and the commencement of the movement of the lever from the base line. Intervals of 100 to the second traced by a tuning fork just below the muscle twitch show that its duration was a little longer than one-hundredth of a second; (2) a period of contraction during which the lever is raised to the highest point; and (3) a period of relaxation during which the muscle returns to its former length.

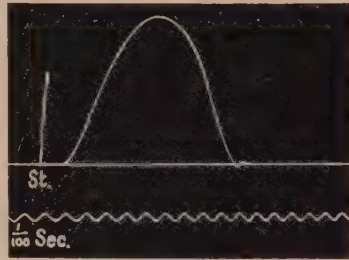


FIG. 4.—Simple muscle twitch.

The vertical line marks the moment at which the stimulus was applied. Below is a time-record, each double vibration representing $\frac{1}{100}$ second.

LATENT PERIOD.—The latent period is partly due to inertia of the lever, which does not commence to move immediately the muscle begins to contract. When this source of error is eliminated the true latent period is found to be about three-thousandths of a second. Careful analysis shows that this is made up of: (a) the time taken for the nerve to convey the impulse from the point which was stimulated to the motor end-organ; (b) the time taken in passing through the motor end-plate; (c) the time required for those chemical events to take place in the muscle which precede and result in contraction.

THE ALL OR NONE LAW.—Very simple experiments show that a certain strength of stimulus is necessary in order to produce visible contraction of a muscle. A slight increase of this stimulus causes the muscle to contract more strongly, a further increase in the stimulus produces a still further contraction, and with additional slight increases the contraction becomes maximal.

This varying degree of contraction to varying strengths of stimulus is due to the fact that while weaker stimuli affect but a few fibres, stronger stimuli affect a larger number. Careful experiments on muscles containing only a few fibres demonstrate the important fact that each fibre, if it contracts at all, gives the maximum contraction of which it is capable. This is known as the "all or none law." It is true of skeletal muscle whether stimulated directly or through its nerve; it is also true of cardiac muscle and of nerve-fibres. In normal life the strength of a muscular contraction is determined by varying the number of fibres which are caused to contract at any one moment.

VELOCITY OF THE CONTRACTION WAVE.—When a muscle contracts, the contraction travels from the stimulated point to other parts of the muscle with a velocity of about 4 metres per second in cold-blooded animals and 6 metres per second in hot-blooded animals. The velocity can be measured by resting a series of levers on the muscle and applying a stimulus to one end. As the wave travels down it will raise the levers in turn, and an analysis of the records they produce will indicate the rate at which the contraction wave was travelling.

EFFECTS OF TEMPERATURE.—It will be seen in Fig. 5 that a rise of temperature quickens, and a fall of temperature

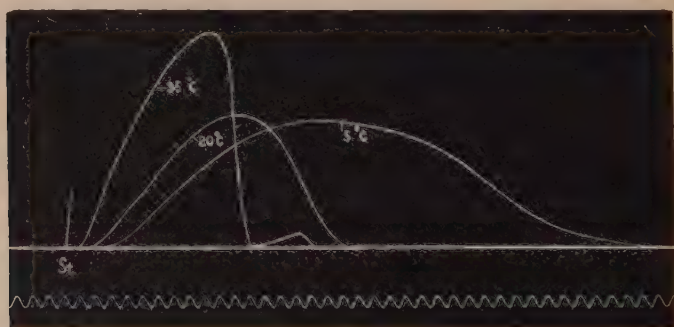


FIG. 5.—Tracing showing the effect of temperature on a simple twitch of the gastrocnemius of the frog. The point of stimulation is the same for each of the three contractions.

delays, every phase in the muscular contraction. The higher the temperature, the shorter is the latent period, the shorter is the time taken for the lever to reach the summit of the contraction, and the shorter is the time taken for the relaxation. Prolonged exposure either to a temperature of 0°C . or to a temperature of 35°C . in time destroys the vitality of muscle.

EFFECTS OF FATIGUE.—If a muscle be repeatedly stimulated, the height of the contractions diminishes. All phases of the contraction are prolonged. Fig. 6 shows the effects of fatigue very clearly.

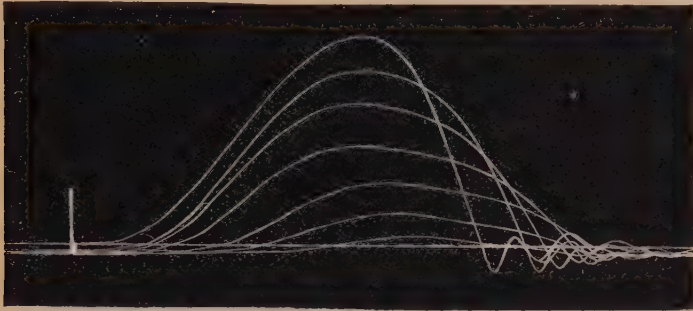


FIG. 6.—Tracing showing the effect of fatigue upon muscular contraction. Every fifteenth contraction is recorded. The muscle was heavily loaded, and fatigue occurred rapidly.

THE EFFECT OF LENGTH OF MUSCLE.—By suitable apparatus it is possible to measure the tension set up in a muscle when it contracts without being allowed to shorten. Curves obtained with such an apparatus are called isometric. As Fig. 7

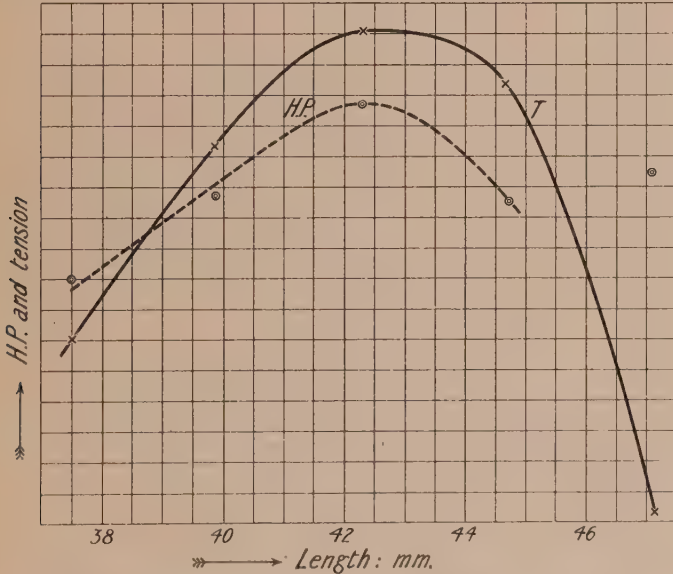


FIG. 7.—To show the effect of alteration of initial length of a muscle on the heat production (dotted lines), and tension developed (continuous line) on isometric contraction. (Evans and Hill.) (*Journal of Physiology.*)

shows, an increase in the length of the muscle at first produces an increase in the tension which is developed, and this increase continues until an optimum value is reached. Beyond this point the tension developed begins to fall. This is an extremely important relationship. It is true of both striated and cardiac muscle. In the former the maximum energy is produced when the muscle has a length which is its normal relaxed length from the body, *e.g.* in the case of the biceps muscle the greatest tension is developed when the arm is straight.

ELASTICITY OF A MUSCLE.—When weights of varying mass are applied to a muscle which is in a relaxed state, it behaves initially like an elastic substance, each additional increase in weight being accompanied by a corresponding elongation. This is the behaviour of a steel spring and is known as Hooke's Law. As additional weights are added, however, the muscle ceases to obey Hooke's Law. The elongations produced gradually become smaller and smaller in comparison with the additional weights put on. If now the weights are gradually removed so that the muscle slowly returns to its unloaded state, it will be found to be definitely longer than it was at first; in other words it has become temporarily stretched. In this respect also it fails to obey Hooke's Law.

EFFECT OF LOAD ON WORK DONE.—There are two different ways in which this matter may be investigated.

Method a: The weight to be lifted is supported until the muscle commences to raise it (a man employs this method when he lifts a weight which is resting on a table). The results obtained are shown in Fig. 8. It will be seen that the height through which the weight is lifted rapidly decreases as the mass of the weight increases. If mass is multiplied by height so as to calculate the work done, it will be found that the work reaches a maximum, then rapidly falls again.

Method b: The muscle supports the weight the whole time, so that each time the mass of the weight is increased the uncontracted length of the muscle increases (a man employs this method when he is supporting a weight with his arm hanging down from his side and he suddenly raises the weight). The results obtained are shown in Fig. 8. It will be seen at once that the height through which the heavier weights are lifted is considerably greater than that by method *a*. For example, 80 grammes was lifted through a height nearly as great as that of 10 grammes using method *b*, whereas using method *a* the larger weight was not lifted at all.

Now the difference between the conditions of the muscles under the two methods is this. In method *a* the weight cannot increase the length of the muscle, whereas employing method *b*

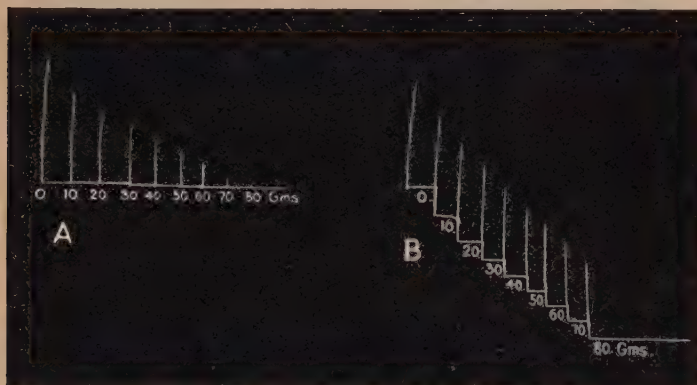


FIG. 8.—Tracing to show the effect of different loads on the extent of contraction of the gastrocnemius of the frog; A, when after-loaded; B, when free-weighted.

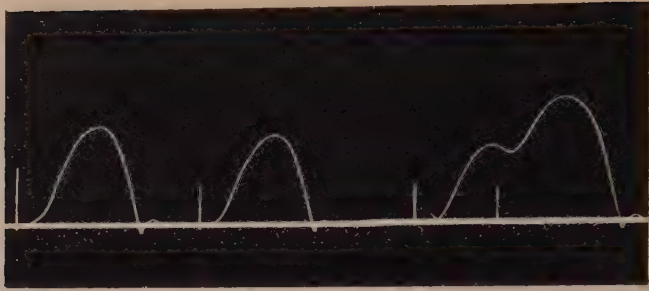
it does do so. We thus find that increasing the length of a muscle, in this case also, clearly increases the work which it is capable of performing.

SECTION III

SUMMATION OF CONTRACTION.—If a second stimulus is sent into a muscle before the lever has returned to the base line after performing a previous contraction, a second contraction takes place which may cause the lever to rise to a height considerably in excess of that which a single contraction would produce. This is shown in Fig. 9. The phenomenon is called *summation of contraction*.

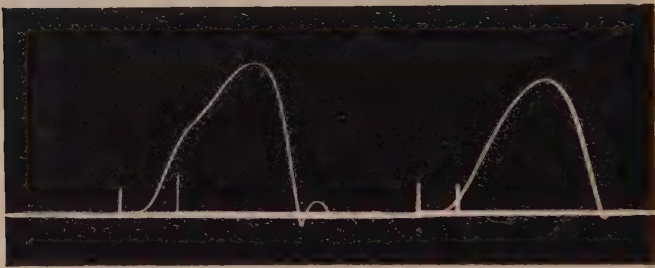
TETANUS.—If the stimuli are rapidly repeated, as the rapidity increases the muscle contracts with increasing rapidity until there is practically no indication that relaxation is occurring between the successive contractions. When this state is reached the muscle is said to have gone into a tetanus. The development of a tetanus is well seen in Fig. 10.

SUMMATION IN CONDUCTION.—Suppose we find by experiment that a certain strength of current of very short duration is required to cause a muscle to contract, and that we now decrease



A

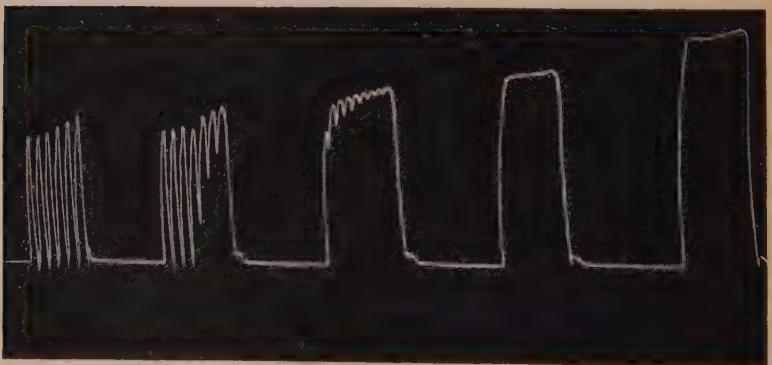
B



C

D

FIG. 9.—Tracing to show summation of muscular contractions (gastrocnemius of frog). From A to D the interval between two successive stimuli was progressively shortened as shown by the points of stimulation marked on the tracing.



1

2

3

4

5

FIG. 10.—Tracing to show the genesis of tetanus. The first group of contractions resulted from the application of ten stimuli per second; in each succeeding group the frequency of the stimuli is increased: the fifth shows complete tetanus. Note the marked contraction of the muscle during tetanus.

this current until a point is reached at which no contraction is visible: experiment shows that two such stimulations are able to produce a contraction of the muscle. They must, however, follow one another very rapidly. The longest time that can elapse between them is known as the *summation interval*. In frog's nerve it is 0·0005, in the sartorius it is 0·0015, and in heart-muscle it is 0·008.

REFRACTORY PHASE.—If a longer time than this is tested, it is found that the second stimulus has no effect whatever. The term refractory phase is applied to this phenomenon. When once a stimulus has set in operation the chemical changes which will result in a muscular contraction, the mechanism refuses to be affected by any further stimuli until this refractory phase is over. In the case of frog's nerve the refractory phase lasts from 0·0005 to 0·003, in the case of the sartorius muscle from 0·0015 to 0·02, and in the case of the heart-ventricle from 0·008 to 0·2. It is of the greatest importance in heart-muscle, as will be shown later, in Chapter V.

CHRONAXIE.—The chronaxie of a muscle is the minimal effective duration of a current which has double the threshold intensity. Possibly the following description will make the matter clear. An apparatus is used which stimulates muscles with currents of known strength for known fractions of a second. A muscle is put in place, the apparatus is put at zero, and the experiment started. Steady currents of very gradually increasing intensity are applied to the muscle until it is seen to twitch slightly for the first time. The strength of this current is carefully noted, for it has the threshold intensity. The pointer of the instrument is now set at exactly double this threshold value, and arrangements are made to apply it to the muscle for various fractions of a second. The duration of each application is increased until the muscle is seen to twitch. This duration is carefully measured; it is the chronaxie of the muscle.

The chronaxie of nerve, skeletal muscle, and heart-muscle are given in the following table (Lucas):—

Frog's nerve	.	.	.	.	.	0·003 second.
Sartorius.	.	.	.	.	.	0·02 "
Ventricle.	.	.	.	.	.	2·00 seconds.

The interesting fact is that chronaxie seems to vary in duration with different tissues, like some other physiological characteristics do.

The shorter the chronaxie (A),
 The shorter the latent period of contraction (B),
 The shorter the refractory period (C),
 The shorter the duration of the isometric twitch (D),
 The shorter the duration of the action current (E),
 The shorter the time taken for the contraction wave to travel 1 c.m. (F),
 The shorter the summation interval (G).

Some of these relationships are shown in the table below :—

	A	C	E	G
Frog's nerve . . .	0.003	0.003	0.0008	0.0005
Sartorius . . .	0.02	0.01	0.01	0.0015
Ventricle . . .	2.00	0.2	2.3	0.008

Somewhat similar relationships have been pointed out by Lewis in the case of the heart tissues :—

	Fibre Size.	Rate of Conduction.	Duration of Systole.	Refractory Period.
Sino-auricular node of heart	1	1	(4)	4
Ventricle of heart . . .	2	2	3	3
Auricle of heart . . .	3	3	2	2
Purkinje fibres of heart . .	4	4	(1)	1

Figures in brackets as yet theoretical.

Lapique has recently suggested that a muscle and the nerve which innervates it have the same chronaxie. He explains the effects of curare on a muscle-nerve preparation on the grounds that their chronaxies are now no longer the same ; for that of the muscle is now too long. Strychnine poisoning he explains on the grounds that the nerve chronaxie has now become too short for the muscle. Veratrine, nicotine, and physostigmine poisoning of muscle-nerve he explains on the grounds that the muscle chronaxie has become too short for the nerve. The effects of fatigue in muscle-nerve he explains on the grounds that the muscle chronaxie has become too long for its nerve. In other words, the effects of fatigue are similar to those of curare. This hypothesis awaits confirmation.

ELECTRICAL CHANGES IN MUSCLE.—When a muscle contracts, various changes occur in it which may be classified as being physiological, physical, and chemical. The physiological changes have been considered in the earlier parts of this chapter. The physical changes are the production of heat and electric currents ; the chemical changes involve the production and removal of lactic acid and CO_2 . These aspects of muscular contraction will now be considered.

If two non-polarisable electrodes be placed in contact with the external surfaces of a frog's muscle, and wires be connected from them to a sufficiently delicate galvanometer, it will be found that muscular contraction is accompanied by the generation of

electric currents which cause the galvanometer to move. Two kinds of galvanometer are used for this purpose: the capillary electrometer which is shown in Fig. 11 will be seen to consist

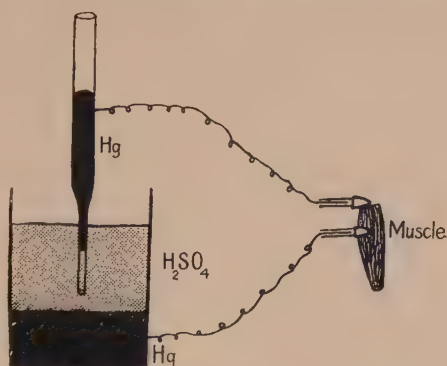


FIG. 11.—Scheme of capillary electrometer.

made extremely sensitive. A highly magnified image of the surface of the meniscus is recorded by a rapidly moving photographic plate. The second galvanometer consists of a tightly stretched silvered quartz fibre. This is suspended between the poles of a powerful magnet. When currents pass through the silver coating, the fibre is deflected in a direction at right angles to the lines of magnetic force. The movements of the fibre are highly magnified and are projected on to a rapidly moving photographic plate. The arrangement is shown in Fig. 12. When one of these apparatus is in use, it is found that

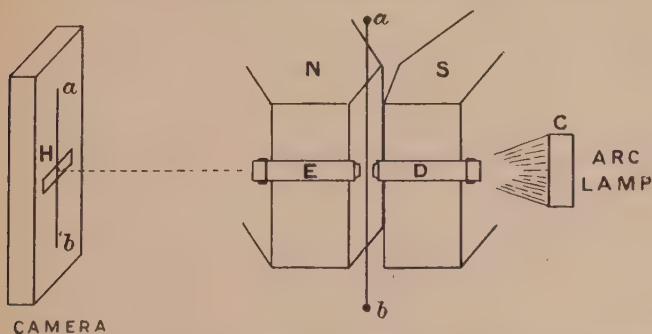


FIG. 12.—Scheme of string galvanometer.

a, b is the quartz thread; *N* and *S* are poles of the electro-magnet; *E* is a microscope. The magnified image of the thread falls on the slit *H*, and is photographed. (Hume.)

an unstimulated muscle produces no detectable current. If now one end of the muscle be stimulated and a contraction wave in consequence be caused to pass down it, the non-polarisable

electrode nearest to the stimulated point first becomes negative to the other. Then, as the wave travels on, both become equally

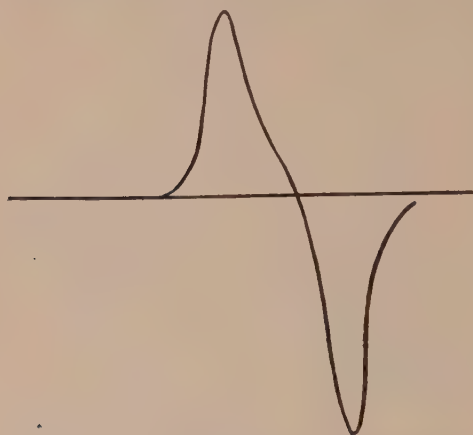


FIG. 13.—Diphasic electrical change in muscle.
(Diagrammatic.)

The horizontal line represents the position of the thread when at rest.

negative. A moment later, when the wave has left the first electrode it becomes more positive to the second one. In consequence the electrical change is that represented in Fig. 13. Since it consists of a galvanometer movement, first to one side and then to the other side of the zero line, it is called a *diphasic response*.

If part of the muscle in contact with one of the electrodes is injured, this part is negative to

all the uninjured portions. In consequence a current flows which is called the *current of injury*.

SECTION IV

HEAT PRODUCTION IN MUSCLE.—It is common knowledge that the temperature of the body rises during muscular contraction. There is ample experimental evidence that this heat is produced in the muscles as the result of contraction. By means of a delicate thermopile it is possible to record electrically the heat produced in small isolated muscles. Hill and his co-workers have recently improved thermopiles to such an extent that the heat changes occurring during and just after a single muscle twitch can be accurately recorded. Such experiments show that heat is produced in two parts: First, initial heat which accompanies contraction and relaxation. This will be evolved in the absence of oxygen. Second, delayed heat which occurs subsequently when contraction and relaxation are over. This requires oxygen and is about $1\frac{1}{2}$ times as great as the initial heat.

CHEMICAL CHANGES IN MUSCLE.—Experiment shows that three important changes accompany muscular contraction: (1) the absorption of oxygen; (2) the excretion of CO_2 ; and (3) the liberation of lactic acid, phosphoric acid, and creatine.

The changes which occur can best be described in two separate stages: First, that which causes the contraction of muscle, and, second, that which restores the muscle to its original condition. The first stage can take place in the absence of oxygen, and consists in the disintegration of hexose phosphate (lactacidogen) into lactic and phosphoric acids. Stage two, which occurs in the presence of oxygen, is the oxidation of one-fifth of this lactic acid with the formation of CO_2 and water. In consequence of this the remaining four-fifths lactic acid are built back once more into the hexose phosphate, thus returning the muscle to its original condition, except for the loss of one-fifth of the hexose phosphate. With regard to this latter process, it is quite possible that other materials may be oxidised instead of the lactic acid, in which case the whole of the lactic acid could be returned to the condition from which it started, and the final condition of the muscle would therefore be identical with its initial state, so far as hexose phosphate is concerned. Hexose phosphate is formed from the glycogen of muscle by some, at present unknown, chemical change.

ANÆROBIC MUSCULAR CONTRACTION.—When an isolated frog's muscle, surrounded by nitrogen, is caused to contract, it will be found to fatigue rapidly. When it will no longer contract we can say that one of two conditions has caused the cessation. Either there is no more hexose phosphate left, nor glycogen from which it can be formed, or so much lactic acid has been produced by the muscular contraction that the muscle has become poisoned. Usually the second is found to be the important factor. The "lactic acid maximum" is said to have been reached. This is usually 0.3 to 0.4 gramme per 100 grammes of muscle. That it is the acid reaction of the muscle which has brought about this stoppage can readily be proved in two ways: (1) if we commence by perfusing the muscle with such a solution that it is made initially acid, then it stops contracting at a much earlier time, and the amount of lactic acid that it contains is small; (2) if we surround the muscle by an alkaline solution from which the O_2 has been removed, *e.g.* 2.4 per cent. alkaline sodium phosphate, we find that the muscle will go on contracting until the whole of its glycogen has disappeared and the lactic acid may then have gone up to as high a value as 0.8 to 1.2 grammes per 100 grammes of muscle.

ÆROBIC MUSCULAR RECOVERY.—If muscles which have been stimulated until they will contract no longer are placed in O_2 considerable quantities are absorbed with the production of equivalent quantities of CO_2 , that is the respiratory quotient

(CO_2 evolved divided by O_2 absorbed) is 1. This shows conclusively that the substance or substances oxidised contain the necessary amount of oxygen in their molecule to combine with the hydrogen which they contain for the formation of water. This is the case with lactic acid, glucose, and glycogen. If some of the muscle is taken for analysis at different stages of the recovery process, it will be found that the amounts of O_2 absorbed and CO_2 eliminated are in correspondence with the quantity of lactic acid which has disappeared. One of two things is possible. Either some of the lactic acid has itself been oxidised with the liberation of energy, this energy being utilised for reconversion of the remainder of the lactic acid into the hexose phosphate complex (lactacidogen), or, alternatively, some other substance of a carbohydrate nature has been oxidised, thus providing the necessary energy for the reconversion of the whole of the lactic acid. In either case there would be a respiratory quotient of 1 and the amount of lactic acid which disappeared would be proportional to the oxygen absorbed and the CO_2 given out. Present-day opinion inclines to the former view, namely, that one-fifth of the lactic acid is oxidised, the remaining four-fifths being built back again for further use.

THERMODYNAMICS OF CONTRACTION.—Experiment shows that when muscle has produced by its contraction 1 gramme of lactic acid, 344 small calories are produced. This is the initial heat which accompanies the contraction. This, as mentioned above, will occur whether the muscle is in oxygen or not. During the following fifteen minutes a further 41 calories are usually evolved. This evolution of heat also takes place in the absence of oxygen. Now, if oxygen be admitted, the recovery process accompanied by the disappearance of the lactic acid is allowed to take place. Then absorption of oxygen and evolution of CO_2 occur and there is a further evolution of 516 calories. If we regard the 344 calories of initial heat as being 1, it will be seen the 516 calories of delayed heat are equal to about 1.5. That is, the ratio of initial to recovery heat is in the ratio of 1 to 1.5. The total calories evolved, therefore, in muscle, when 1 gramme of lactic acid has been formed and subsequently disposed of, are 860 ($344 + 516$). Now if the whole of the lactic acid had been oxidised, the heat evolved would have been 3836 calories, which is nearly the same as the heat of combustion of 1 gramme of glycogen dissolved in water. If, then, we oxidise 0.22 gramme of either lactic acid or glycogen, we have evolved approximately 860 small calories, which is sufficient to provide for the 344 calories of initial heat and the 516 calories of delayed heat

necessary for the reconversion of the lactic acid into its initial condition.

WORK AND EFFICIENCY OF MUSCLE.—The muscles which have been considered in these sections on heat production were prevented from performing any external work. This was done in order that the whole of the heat might appear in a form readily estimated by means of the thermopile. But, if we make the muscles do the maximum work of which they are capable, the whole of the initial heat can appear as external work, and only the ærobie delayed heat (516 small calories) appears actually in the form of heat. We are therefore in a position to calculate at once the maximum efficiency that a muscle is capable of attaining. Of the total 860 small calories, 344 can appear as work. This works out at precisely 40 per cent. It is interesting to compare this figure with that obtained by Hill and his co-workers on trained athletes. They found that the maximum efficiency obtainable was between 38 and 39 per cent.

MUSCULAR FATIGUE.—The fatigue which is observed experimentally in an isolated frog's muscle may be due either to the exhaustion of the glycogen and hexose phosphate, or to the accumulation of lactic acid. That the latter is an important factor can be shown by the fact that fatigue can be induced in perfectly fresh muscle if the latter be perfused with blood containing lactic acid. The feelings of fatigue which we ourselves experience when we are tired may be due to the painful stimuli aroused in our muscles by the increasing acid reaction produced by the rise in the lactic acid content. That some chemical process or other affects the motor end-organ can be shown by stimulating a muscle directly after it is showing marked signs of fatigue when stimulated via its nerve. It is found that the muscle shows less signs of fatigue, clearly indicating that some of the appearances of fatigue were due to the motor end-organ. As mentioned above, under the section on chronaxie, Lapique considers that this is due to the development of a difference in the chronaxie of the muscle and its nerve which might very easily be due to chemical changes, seeing that similar differences of chronaxie may be brought about by drugs.

RIGOR MORTIS.—When a muscle dies naturally, through want of oxygen, or is killed, *e.g.* by dropping in boiling water, it shortens slightly, becomes rigid and opaque, and loses its elasticity. Chemical analysis shows that it contains lactic acid; it is also found that heat is evolved. These changes are all due to the

breaking down of the hexose phosphate with the liberation of lactic acid. The lactic acid reacts with the sodium bicarbonate in the muscle, and in consequence CO_2 is given off. It also reacts with the proteins of the muscle, causes them to coagulate, and thus alters their physical condition. If the muscle were rendered more acid before the onset of rigor mortis it is clear that the phenomenon would be accelerated. It is for this reason that the muscles of the fatigued animals pass into rigor mortis more rapidly after death than the muscles of rested animals.

SECTION V

HISTOLOGY OF UNSTRIATED MUSCLE.—The fibres composing smooth muscle are much smaller than those of striated. They vary greatly in length, and do not show the cross-striation which is a conspicuous feature of striated muscle. They do show, however, a fine longitudinal striation. Each cell has an oval or rod-shaped nucleus with one or two nucleoli. Between the fibres is a little cement substance which can be stained by silver nitrate. It is found in the walls of practically all the tubular structures of the body, *e.g.* the lower part of the oesophagus, the stomach, and the intestines, in the trachea, bronchi and bronchioles, in the ureters, the bladder, and the urethra, in the Fallopian tubes, the uterus, and the vagina, in the spleen and lymph glands, in Tenon's capsule of the eye, in the muscles of the iris and accommodation, in the skin, arteries, arterioles, and veins. Under experimental investigation it is found to show, in favourable circumstances, a great many of the phenomena which are characteristic of striated muscle. Everything, however, takes far longer. The latent period may be 0.4 second, the contraction may take a minute. The stimuli for smooth muscle are essentially the same as for striated. Smooth muscle exhibits the phenomenon of summation of stimuli extremely well, as the contraction travels as a wave from one end of the muscle sheet to the other. Smooth muscle is extremely susceptible to changes of temperature. On cooling to about 5°C . it enters into continuous contraction. As a rule, rise of temperature produces relaxation until about 40°C . is reached. It then undergoes a marked heat contraction which passes off when death occurs at a temperature a little above this.

THE METABOLISM OF SMOOTH MUSCLE.—This exhibits some interesting phenomena. There is reason to believe that smooth muscle can remain in tone for long periods of time with a consumption of very small amounts of energy. Thus, shell fish

like the oyster can close their shells and keep them closed in spite of the steady application of forces tending to pull them open for, apparently, hours on end, with the absorption of but small amounts of oxygen and the evolution of but small amounts of CO_2 and heat. This behaviour has been called "catch action." Recent work has shown that the extremely long period of time occupied by a contraction in smooth muscle is really responsible for the phenomena observed. Impulses of perhaps four per minute would cause a tetanus in such slowly relaxing muscle. The expenditure of energy would, therefore, be a small fraction of that required to produce a tetanus in a skeletal muscle for the same length of time. It is found, further, that two nerves run to this smooth muscle. Stimulation of one of these causes contraction, and the muscle will remain contracted even if this nerve be divided. The other nerve, on the contrary, when it is stimulated, causes immediate relaxation, enabling the shell to be opened. This behaviour also strongly suggests a catch mechanism, the stimulation of one nerve lowering the catch and preventing the shell from being opened, the stimulation of the other nerve releasing the catch and permitting opening.

SECTION VI

MOVEMENTS OF CILIA.—Histologically, ciliated cells are seen to consist of a columnar or cubical cell body, a spherical or oval nucleus, and a large number of fine parallel but separate filaments or cilia which project usually at right angles to the free surface which the ciliated cell is forming with its neighbours. Sheets of these cells are found lining the Fallopian tubes, in the uterus, in the epididymis, in the central canal of the spinal cord, inside the cerebral ventricles, in the nasal cavity (the olfactory cells seem to be modified ciliated cells), down the whole length of the trachea, and in the bronchi and bronchioles.

CONCERTED ACTION.—If a sheet of ciliated cells be examined, it will be seen that a wave of movement travels down from one end of the sheet to the other, not unlike the waves which travel over a field of corn. Clearly there is concerted action between neighbouring cells. Looked at individually, the cilia appear to move from right to left in a more or less bent position. Then each cilium erects itself, and in the erect position travels from left to right. Once more it bends down and the whole cycle is repeated. All the cilia attached to one cell make synchronous movements. This movement is repeated approximately once per second. It seems to be entirely automatic, being unaffected

by the stimulation of neighbouring nerves. One essential condition appears to be, however, that the cilia should be well lubricated by mucus. This condition is satisfied by the secretion of numerous glands lying under the ciliated epithelium.

THE OBJECT OF CILIARY MOVEMENT is to produce slow continuous movement in structures which otherwise would be motionless. For example, fine particles of grit, passing in through the nose or mouth with each inspiration, settle sooner or later on the ciliated epithelium and are swept by the cilia in a steady stream towards the mouth cavity, entangled in little masses of mucus. On entering the mouth cavity they are suitably dealt with according to our habits.

CAUSE OF CILIARY MOVEMENT.—The precise nature of ciliary movement is not known. The following hypothesis is as probable as any other. The cilia themselves are easily bent filaments; along one edge of the filament is attached a narrow inextensible membrane. This permits the filament to bend readily towards the side on which the membrane is attached, since the membrane can fold up, but prevents it bending in the opposite direction unless the membrane is torn. These cilia are inserted with their membranes all on the same side through holes in the cell wall, and their lower ends are inserted into the protoplasm of the cell. If now osmotic pressure by the liberation of chemical substances increases on one side of the cell, and by the synthesis of chemical substances disappears on the other, water will be absorbed on one side and will disappear on the other; in consequence the protoplasm of the cell as a whole will be shifted one way. This will move the lower ends of the cilia and will cause them to bend, the holes through the cell wall behaving like rowlocks. On reversing the osmotic effects, the cell protoplasm will move in the opposite direction, and the cilia be in consequence moved in the opposite direction to what they were before. Thus to-and-fro movement in all the cilia will be brought about at the same time, and since the cilia bend as they go one way, but not as they go the other, because of the membrane attached to them, the movements described in the section on concerted action will be produced.

CHAPTER III

NERVE

SECTION I

NEURONES.—The whole nervous system is composed of chains of *Neurones*, all conveying, so far as is known, the same kind of impulse. Each neurone consists of a nucleated *nerve-cell* and its branches. Branches which are short, rough, and contain Nissl substance, are called “dendrites.” Those that are long and smooth are “axons.” It is the function of the terminal ends of both dendrites and axons to connect with either (*a*) sensory end-organs, (*b*) the dendrites or axons of other nerve-cells to form a synapse, or (*c*) the motor end-plates of muscles.

NERVE-CELLS.—The following are the histological characteristics of nerve-cells. The cells are usually large; the nucleus is usually large and spherical, and with a well-marked nucleolus. The cell protoplasm when stained with methylene or toluidine blue shows the presence of Nissl substance. The cell protoplasm when suitably stained also shows fine neuro-fibrils running from dendrons to axons. These usually interlace, forming a neuro-reticulum. All nerve-cells have a clear cell wall; sometimes there is, in addition, a capsule. Fine channels, probably for nutrition, are seen penetrating the protoplasm. The cells differ considerably in shape and size according to the number and nature of their processes. Some typical examples will shortly be given.

DENDRITES.—These are protoplasmic processes which, leaving the cell at a root, proceed to branch into fine and yet finer subdivisions. Usually they appear to ramify in undifferentiated protoplasm. Into this same protoplasm are ramifying the dendrites of other nerve-cells or the terminal ends of their axons. The dendrites of one cell thus become very intimately associated with the processes of other cells. The whole structure thus formed is called a synapse. The functions of this important structure

will be discussed later. Here it suffices to say that according to circumstances the synapse may conduct freely nerve impulses from one cell to another (conduction) or it may not (inhibition). When one impulse has got through, others following it may get through easily (facilitation). On the contrary, others may find increasing difficulty (refractory phase).

AXONS are modified dendrites in that the root is long, and the fine terminal ends are placed at some distance from the nerve-cells. Sometimes no processes are given out along the length of an axon. Sometimes they are, and are then known as collaterals. Axons may be long (nearly a metre) or medium, or short (fractions of a millimetre). They may be large or small in diameter, non-medullated or medullated (see below).

TYPES OF NERVE-CELLS.—Nerve-cells may be divided initially into those with no axons, those with one axon, and those with two axons. Those with no axons possess dendrites only. They are mostly used for connecting a number of synapses so that they may operate together. Those with one axon invariably possess dendrites as well. All motor nerves are examples. The impulse passes from dendrites through the nerve-cell to axons. It is clearly possible, by mere inspection, to state the direction which nerve impulses will be taking. Those with two axons may possess no dendrites. Most sensory nerves are examples. The impulse in these travels towards the nerve-cell along one axon and away from it along the other. It is clearly impossible, therefore, by mere inspection to say in what direction the impulse is travelling.

NERVE-FIBRES.—A nerve-fibre is the axon of a neurone. It consists of a finely striated central core or axis-cylinder which is surrounded, in the case of a non-medullated fibre, by a simple sheath of connective-tissue cells. If, however, the fibre is medullated, in addition to a more complex connective-tissue sheath, there is a surrounding tube of fatty material called myelin. This material shows histologically the typical staining reactions of fats, *i.e.* it stains yellow with Sudan III and Scharlach R. It also shows the presence of unsaturated fats by reducing osmic acid with the production of a black stain in the myelin. This fatty semi-liquid material lies between two connective-tissue coats, one very thin and in close apposition to the axis-cylinder, the other somewhat stouter, forming the outside of the fibre as a whole. This connective-tissue envelope, called the neurolemma is formed from flattened nucleated connective-tissue cells.

THE NODES OF RANVIER.—This neurolemma with its contained myelin forms short, butt-ended sections, there being a small uncovered length of axis-cylinder where one short section of sheath stops and another one commences. Not only can food material and oxygen reach the axis-cylinder at these points, but other substances can as well. For example, if a few such fibres after previous washing with sodium sulphate be immersed in silver nitrate in a strong light, metallic silver is deposited in the axis-cylinder where these nodes occur. Other parts of the axis-cylinder are inaccessible to the silver nitrate solution because of the presence of the medullary sheath.

THE NUTRITIVE FUNCTION OF NERVE-CELLS.—Since it is the function of the axis-cylinder to conduct the nerve impulse, the function of the nerve-cell may be questioned. That the cell does not play an essential part in nerve conduction is shown by the fact that axis-cylinders from which nerve-cells have been removed will continue to function in suitable circumstances for many hours. On the other hand, there is ample evidence that in the intact animal the nerve-cell has three highly important functions: (1) it is from the cell that the axis-cylinder develops in the embryo; (2) the nerve-cell is responsible for the continued existence of the axis-cylinder (the effects of separating axis-cylinders from their nerve-cells will be considered in the section which follows); (3) when repair is effected in a damaged nerve, it is from the nerve-cell that this repair originates.

DEGENERATION OF NERVE.—When a mixed nerve is cut or damaged in such a way that the axis-cylinders are separated from their nerve-cells, these axis-cylinders exhibit the histological changes which are called degeneration. The axis-cylinders cut off from their nerves are able to conduct impulses at first; after two to five days this ability disappears. The degenerative changes show themselves in both nerve-cells and axis-cylinders. The nerve-cell swells, its Nissl substance disappears, its dendritic processes become knobbed, its nucleus stains less well. If regeneration is not effected in, say, twelve months, the cell slowly shrinks, and in the course of time will disappear. That part of the axis-cylinder which is on the same side of the cut as the nerve-cell, undergoes degenerative changes as far up as the next node of Ranvier. Precisely similar changes occur in that part of the axis-cylinder on the opposite side of the cut to the nerve-cell. These are: (1) the axis-cylinder loses its fine striation; small pieces near its edge disintegrate and disappear. Since this

process takes place in an irregular manner the previously straight axis-cylinder now appears contorted. Material continues to disappear until the axis-cylinder is discontinuous. The short lengths continue to disintegrate. (2) The neurolemma cells which form the medullary sheath separate from their neighbours, withdraw from the damaged nerve, leaving the medullary substance

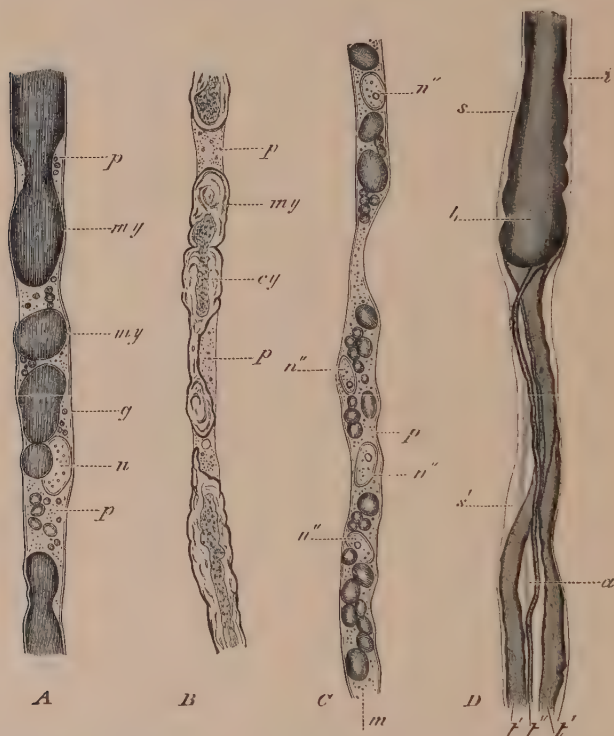


FIG. 14.—Degeneration and regeneration of nerve-fibres in the rabbit. (Ranvier.) (From Schafer's *Essentials of Histology*.)

A, part of a nerve-fibre in which degeneration has commenced in consequence of the section, fifty hours previously, of the trunk of the nerve higher up; *my*, medullary sheath becoming broken up into drops of myelin; *p*, granular protoplasmic substance which is replacing the myelin; *n*, nucleus; *g*, neurolemma. *B*, another fibre in which degeneration is proceeding, the nerve having been cut four days previously; *cy*, axis-cylinder partly broken up. *C*, more advanced stage of degeneration. *D*, commencing regeneration of a nerve-fibre. Several small fibres, *t*, *t'*, have sprouted from the somewhat bulbous cut end, *b*, of the original fibre; *a*, an axis-cylinder which has not yet acquired its medullary sheath; *s*, *s'*, neurolemma of the original fibre.

to aggregate into irregular droplets under the action of surface tension. (See Fig. 14.) The medullary substance commences to break down with the liberation of phosphorus compounds. (3) Phagocytes and wandering connective-tissue cells surround the

degenerating nerve, the blood-vessels in the vicinity become dilated. (4) The white corpuscles, connective-tissue cells, and neurolemma cells engorge themselves with broken-down masses of axis-cylinder and medullary substance, removing them piecemeal. (5) The connective-tissue cells and leucocytes depart, leaving a few scattered neurolemma cells which form a rough chain indicating the course once taken by the axis-cylinder.

REGENERATION OF NERVE.—Before the above stages have reached their termination, fine processes begin to grow out from the cut end of the undegenerated axis-cylinder which, as mentioned above, is connected with its nerve-cell. These processes have little knob-like swellings at their ends. They sprout in all directions until one finds the course of the old nerve when it proceeds down between the neurolemma cells; the other shoots are absorbed, the growth continues between the neurolemma cells, a new axis-cylinder being formed. The neurolemma cells multiply, form a fresh nerve sheath, myelin develops within the sheath, the nodes of Ranvier reappear, and the continuity of the axis-cylinder is once more established. The nerve-cell recovers its Nissl substance, its dendritic processes lose their swellings, and anastomose once more with the dendrites of neighbouring nerve-cells. This process may take a few months or many months according to the length of nerve which has degenerated.

MIXED NERVE.—A mixed nerve, *e.g.* that going from the central nervous system to a limb, consists of axons, some medullated, some non-medullated, some large in diameter, some small, some conveying impulses from the central nervous system to the limb, setting muscles in motion, controlling the secretion of glands, altering the calibre of blood-vessels, some conveying impulses from the limb to the central nervous system, conveying sensory impulses from the end-organs in the skin, conveying impulses from muscles, joints, tendons, bones, informing the central nervous system of limb position, etc. Such a mixed nerve has a surrounding external sheath called the *epineurium*. The interior of this is divided into a number of separate funiculi, which are bound together by a *perineurium*. Each funiculus is composed of a number of axons which are bound together by *endoneurium*.

SECTION II

STIMULATION OF NERVE.—Nerves may be stimulated in a variety of different ways. Mechanically by pinching or hitting; chemically by the application of common salt, also by heating and

drying; lastly, by electric currents. As in muscle, the latter is the most convenient for experimental purposes. Now two phenomena follow one another in the above process: (1) the stimulus sets up a change in the nerve which is expressed by saying that the nerve is excitable. (2) Following this, is the process by which the nerve conducts an impulse. There is reason to

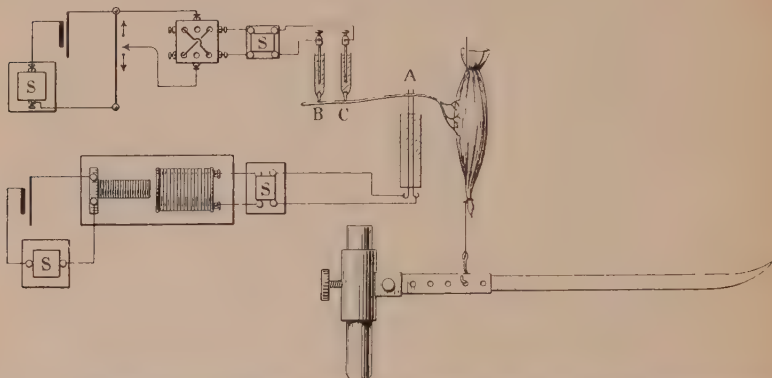


FIG. 15.—Diagram of apparatus used to ascertain the effect of a direct current on the excitability of a nerve. The electrodes B and C apply the direct current. Either B or C could be made the kathode. The electrodes A apply the testing current from the induction coil. The effects are shown in Fig. 16.

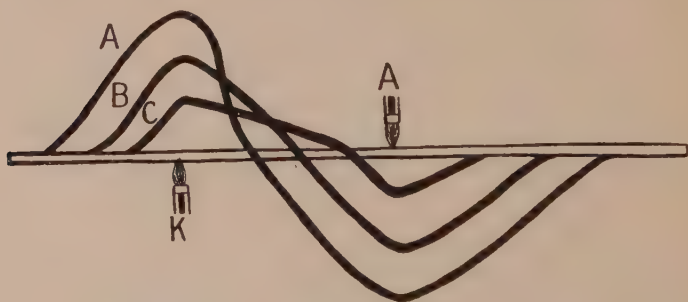


FIG. 16.—Diagram to show changes of excitability in a nerve: A, with strong; B, with medium; C, with weak current, passing from anode A to kathode K.

think that these two processes differ in important respects. For example, if a constant electric current be passed through a nerve, in at one electrode and out at another a short way off, while the current is passing the region of the nerve on either side of the negative electrode is more easily stimulated than it was before, *e.g.* a smaller stimulus will suffice. (See Figs. 15 and 16.) On the contrary, the conduction of an impulse down the nerve may be interrupted by the passage of the same current.

A number of conditions affect the excitability of a nerve. (1) A rise of temperature makes the nerve less irritable and *vice versa*. (2) As has been mentioned above, the passage of a constant current causes the nerve to be more excitable near the negative electrode. (3) By means of the apparatus in Fig. 17 it may

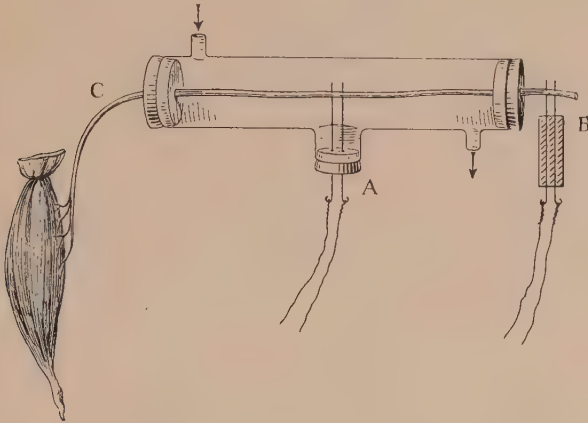


FIG. 17.—Diagram of chamber used to test the effect of gases or volatile drugs on nerve. A, electrodes used to test changes in excitability; B, electrodes used to test changes in conductivity.

be readily shown that carbon dioxide and chloroform vapour, and ether vapour, all reduce the excitability of nerve. The irritability may be restored if fresh air or oxygen be admitted. Lastly, (4) the removal of oxygen destroys the excitability of a nerve which may, however, still be able to conduct a nerve impulse.

CONDUCTION OF NERVE.—The nerve impulse is found to travel with a velocity of approximately 28 metres per second in frog's nerve at laboratory temperature, and approximately 120 metres per second at blood temperature. This velocity is determined by means of the apparatus shown in Figs. 18 and 19. With the two-way key the sciatic nerve of the frog may be stimulated at either A or B. The difference in the duration of the latent period being ascertained from the resulting tracings, and the distance between A and B being known, the time taken for the nerve-impulse to travel from A to B can be readily calculated. It is accompanied by physical, electrical, and chemical changes. The physical changes are the production of heat and the generation of electric currents. The rise of temperature is very small. Thermopiles, consisting of very large numbers of junctions, were

used by Hill for measuring the rise of temperature which took place. The electrical changes are easily demonstrated by means of the capillary galvanometer, particularly if thermionic wireless

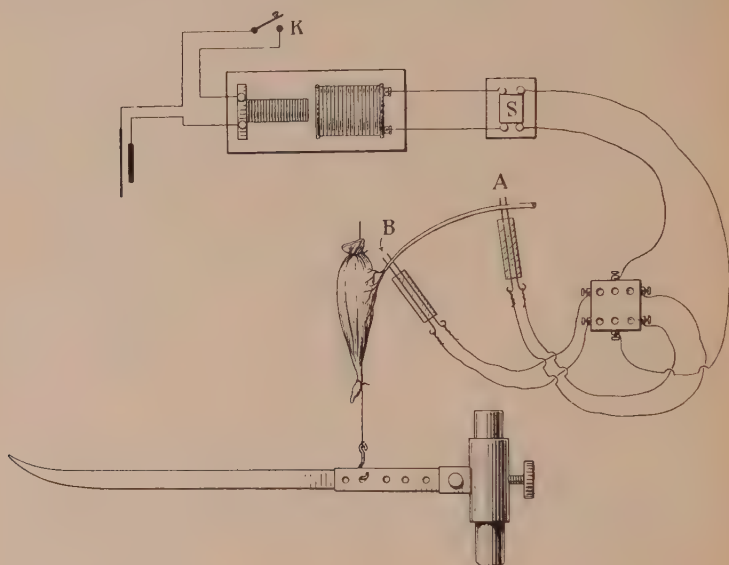


FIG. 18.—Diagram of apparatus used to ascertain the rate of conduction of a propagated impulse in a nerve. K, key; A and B, the two pairs of electrodes, which are used alternately.

valves are used in cascade to amplify the current. The chemical changes which accompany the conduction of a nerve-impulse are



FIG. 19.—Tracing to show how the rate of conduction of a propagated impulse in a nerve is measured. The length of nerve between the two pairs of electrodes measured 45 mm. Time tracing, each vibration = $\frac{1}{100}$ second.

small in magnitude, consisting of an absorption of oxygen and an evolution of CO_2 . Signs of fatigue cannot be demonstrated in a nerve so long as it has an adequate oxygen supply. If the

apparatus in Fig. 20 is used, two nerves are stimulated by the same pair of electrodes, the conduction of one nerve being prevented by freezing at the point marked black on the right-hand nerve. Then tetanising currents may be applied until the left-hand muscle is completely fatigued and shows no sign of contraction. On allowing

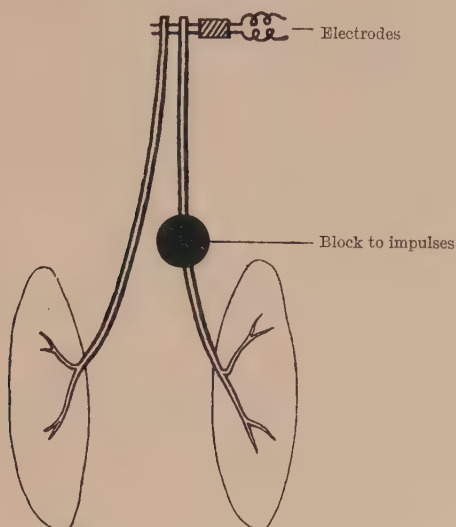


FIG. 20.—Diagram showing method of demonstrating non-fatiguability of nerve-fibres.

the right-hand nerve to thaw, so that it conveys impulses down to the muscle, the same strength of contraction is obtained from the muscle as is given on placing electrodes on the nerve below the block. This shows that the part of the nerve above the block which has been conveying impulses during the whole course of the experiment, has done this without observable fatigue.

CONDUCTION IN BOTH DIRECTIONS.—By stimulating a nerve first at one end and then at another, and by recording the electrical changes in the nerve, which are diphasic as they are in muscle, it can be readily shown that a nerve can conduct with equal facility in both directions. Similar observations on a sensory nerve, which consists of two axis-cylinders with a nerve-cell interposed between them, demonstrate the fact that the nerve-cell does not stop the two-way conduction of the nerve-impulse. Since we find that neurones when arranged in series, as they are in the central nervous system, will only conduct one way, we are forced to the conclusion that this one-way conduction

is a property of the synapse and not a property of any part of the neurone. This important fact will be referred to again in Chapter X.

ALL OR NONE LAW.—We have already referred to the obedience by muscle of the “all or none law.” We shall have to refer to this same law when in Chapter V we deal with cardiac muscle. It is easy to show that nerve obeys the same law by applying stimuli of different strengths and by recording the resulting electrical changes in the nerve. If we are justified in concluding that the electrical changes are a measure of the strength of the impulse which the nerve is conveying where the recording electrodes are touching it, and there is ample experiment that that is the case, we may use this fact for testing obedience to the “all or none law.” On applying varying strengths of electrical stimulus to the nerve we find either no electrical variation further down the nerve or one of constant dimensions, which indicates that the nerve obeys this law.

TRANSMISSION OF VARIATIONS OF INTENSITY.—If nerve obeys the “all or none law,” it may well be asked how variations of intensity are transmitted. How, for example, do we recognise the difference between a small pain and a big one? Or how do we with our fingers at one moment regulate our watch and at the next crack a walnut? The answer is: (a) by variations in the rate at which the all or none impulses follow one another down any one nerve; and (b) by variations in the number of nerves affected. A slight pain or a weak muscular contraction involves few fibres and few impulses. A severe pain or a forceful contraction involves many fibres and torrents of impulses.

CONDUCTION THROUGH A DECREMENT.—By making use of a similar apparatus to that in Fig. 17, we may apply alcohol-vapour to a section of nerve and ascertain by the electrode A the strength of the electric response which is set up in the alcoholised nerve as the result of a stimulus applied at B. It is found that the electrical variation has dimensions smaller than the normal, the size depending on the strength of the alcohol-vapour used. If now, with the nerve still under the influence of alcohol, we ascertain what the dimensions of the electrical changes are, outside the tube, on the opposite side to B, *i.e.* at C, we find that they have returned to the normal size. That is, that the nerve-impulse, which was greatly reduced in strength as the result of the effect of the alcohol-vapour, had returned to the normal size before it reached the muscle. This is a most important observation,

because it shows that so long as an impulse, no matter how small, manages to get through damaged nerve and reach normal nerve, under the influence of the "all or none law" the impulse returns to its normal value. Another point where this is probably important is at a synapse where the terminals of one nerve may be distributed to the dendrites of a large number of nerve-cells. Each of these cells will clearly receive only a fraction of the impulse which was being passed down to the group. Under the influence, however, of the "all or none law," each separate neurone transmits an impulse of the same intensity as it would do if it were the only neurone affected. In this way, important economy can be exercised in the conducting paths of the central nervous system. It is theoretically possible for one axon to affect a large group of new axons and thus to set into operation a large muscle.

REFRACTORY PHASE.—We have described above when dealing with muscle the relationship which exists between chronaxie (A), latent period (B), refractory period (C), duration of isometric twitch (D), duration of action current (E), time taken for impulse to travel (F), and summation interval (G). The shorter the chronaxie, the shorter the others. For example :

	A	C	E	G
Frog's nerve . . .	0·003	0·003	0·0008	0·0005
Sartorius . . .	0·02	0·01	0·01	0·0015
Ventricle . . .	2·00	0·2	2·3	0·008

If then a nerve be stimulated twice within 0·0005 sec. both stimuli are effective because they have occurred during the summation interval. If, however, the second one occurs between 0·0005 and 0·003 sec. after the first, it falls during the refractory period and is lost.

SUPER-NORMAL PHASE.—Whereas muscle, at the end of the refractory period, returns nearly to its normal condition, nerve exhibits an entirely novel effect which is called enhancement. If a second stimulus falls during the period which follows the refractory phase, the intensity of the resulting stimulus is markedly in excess of the usual value. How precisely this enhancement is brought about is not known. Its advantages are, however, quite clear. A tetanic contraction is brought about as we have said above by a rapid succession of separate impulses, each of which obeys the "all or none law." If each succeeding nerve-impulse occurs during the super-normal phase of the one which preceded it, these impulses will reach their respective muscles with a greater strength than single isolated impulses would do.

THE NATURE OF THE NERVE-IMPULSE.—We may summarise the known facts with regard to the nerve-impulse as follows : It travels at a great speed ; a comparatively short length of nerve is affected at a time ; it is accompanied by evolution of minute quantities of heat ; very small amounts of oxygen are absorbed and CO_2 given out. There is a marked electrical change. The fact that the latter is marked and all the others small has suggested that the surface of the nerve may be the seat of the process. Changes which affect surfaces may therefore be expected to take part in the phenomenon, such as osmosis and surface tension. The former can be ruled out on the ground that it would take too long. With regard to the latter, we may advance some such hypothesis as this : Between the axon and the surrounding fluid is a surface layer so that surface tension is developed between them. On stimulation, the surface tension is locally increased ; in consequence this piece of nerve is for a short time electrically different from the parts on either side. An electric current commences to flow out from nerve to liquid where the surface tension is low, and back again from liquid to nerve where the surface tension is high. This electric current acts in its turn as a stimulus to the next section of nerve. In consequence the surface tension of this piece is raised, another battery is set up, the currents produced by which affect the next section and so on, until the far end of the nerve is reached, or it communicates with, *e.g.*, a motor end-organ. Such a hypothesis would fit in with the rapid rate of conduction of the nerve-impulse, the large electrical change, and the small energy changes involved.

EFFECTS OF SALTS.—Experiments show that there is the same kind of salt balance for nerve that is exhibited by most physiological tissues. The salts taken as a whole must have the right osmotic pressure, and the usual salt balance must be preserved, in order that the activity of the nerve shall persist. Strong sodium chloride sets up spontaneous impulses in the nerve to which it is applied ; drying produces a similar phenomenon.

EFFECTS OF DRUGS.—When dealing above with conduction through a decrement, we mentioned that alcohol-vapour reduced the magnitude of the nerve-impulse. The same thing is true of alcohol in solution ; ether and chloroform behave in a similar manner. CO_2 also adversely affects nerve-conduction, so does an acid reaction of the fluid bathing the fibre. Curare, which has a most potent effect on the neuro-muscular junction, has apparently no effect whatever on nerve itself.

SECTION III

PROPERTIES OF THE SYNAPSE.—A synapse may be defined as the undifferentiated protoplasm which is interposed as an intervening layer between the dendritic endings of one nerve and those of another. As we mentioned previously in this chapter, it has the extremely important function of conducting in one direction only. It has a number of other interesting properties. Part of the time taken for an impulse to pass down from the higher centres to the muscles in the carrying out of a voluntary action is occupied by passing through the synapses. Wundt estimated that the time taken for the nerve-impulse to pass across the synapse in the frog to be 0·004 second.

LOCALISATION.—In spite of the fact that histologically one nerve-fibre may appear to be connected by synapses with a number of nerve-cells, physiologically communication may exist between a much smaller number. This clearly indicates that while the necessary structural elements for conduction may be present, some paths may be permanently closed owing to the refusal of the synapse to conduct. This limitation of paths is known as localisation.

INHIBITION.—As a modification of the complete stoppage of all impulses, which we have described in the last section, there may be temporary inhibition. For example, a dog may be walking along when a stimulus producing a tickling sensation is applied to his flank. He immediately sits down, raises the hind leg, on the stimulated side, and proceeds to scratch the affected spot. The impulses producing walking have been temporarily inhibited by those required for the production of the scratch reflex.

FACILITATION.—Suppose now that the stimulus be removed and the dog be allowed to walk a few steps. On reapplying the stimulus to the skin, the scratch reflex will be initiated in a shorter time than it was at first. The more often this experiment is repeated, the quicker is the scratch reflex initiated. This phenomenon is called facilitation. The effects on the synapse are these: that when once its resistance has been overcome, the employment of the path it has laid open results in the synapse resistance being reduced, thus permitting the path to be employed with greater ease.

SUMMATION.—The following experiment will demonstrate the existence of summation in synapses. The stimulation of a small skin area by, for example, a weak stimulus may produce no appreciable sensation. On the other hand, if this weak stimulus

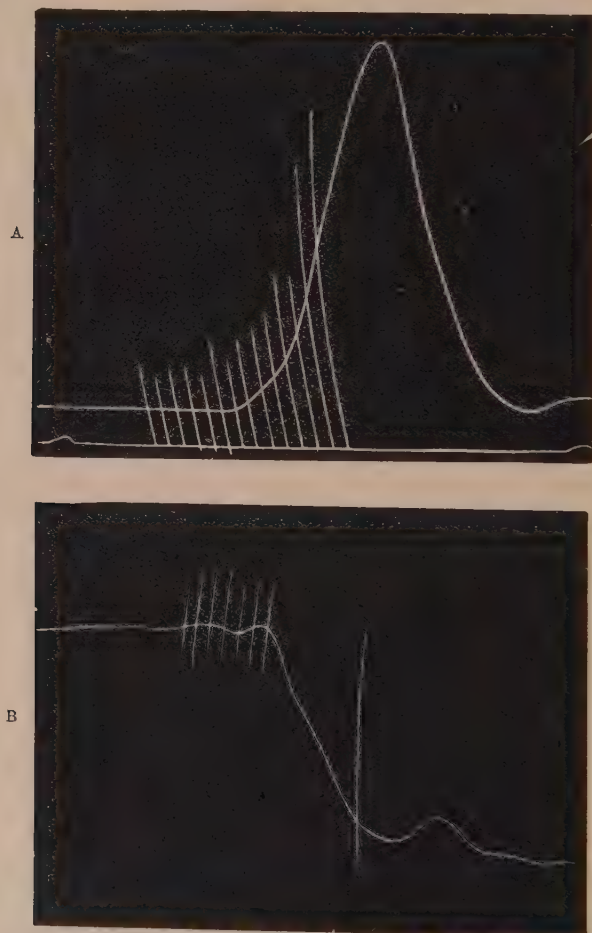


FIG. 21.—Reflex produced by summation of weak stimuli. (Sherrington.) (From Starling's *Principles of Physiology*.)

A, Reflex contraction of flexor muscles of knee. B, Reflex inhibition of extensor muscle. In each case the effect follows the sixth stimulus, the stimuli being applied to the central end of the internal saphenous nerve.

be applied a number of times, it has a cumulative effect so that the resistance of the synapses is finally broken down, the impulse gets through, and results in suitable action. (See Fig. 21.)

CHAPTER IV

THE BLOOD

SECTION I

THE CELLULAR ELEMENTS.—All the cells and tissues are in intimate relationship with capillary vessels, through which blood is continually flowing. Both tissue element and outer wall of capillary are bathed with a fluid called lymph, and a constant interchange of material takes place through the lymph between the tissues and the blood. On the one hand, nutritive substances and oxygen pass from the blood to the tissues to furnish a source of energy and to repair loss of substance, and, on the other hand, carbon dioxide and other waste materials pass from the tissues to the blood. An exchange of water and salts also takes place by diffusion through the capillary wall. In some organs certain substances, called hormones, are supplied to the blood, and are carried in it to the cells or muscle-fibres which they are destined to influence. Further, as the blood circulates, now through muscles and glands in which heat is produced, now through other structures in which heat is lost, it serves to equalise the temperature of the different parts of the body.

FRESHLY SHED BLOOD.—This is a red, viscid, opaque fluid with a specific gravity of 1059. The specific gravity may be ascertained with a single drop of blood by making a mixture of chloroform and benzol, and finding the proportions of the two fluids in which a drop of blood remains suspended without tending either to sink or to rise. The specific gravity of the mixture, ascertained by means of a hydrometer, is that of the blood itself.

When human blood is examined under the microscope, it is seen to consist of two kinds of corpuscle floating in a pale yellow fluid, the blood-plasma. There are about 5,000,000 red blood-corpuscles, or erythrocytes, in every cubic millimetre of blood. Of the other variety of corpuscle, the white blood-corpuscle, or leucocyte, there are about 9000 in every cubic millimetre of blood. That is, they are present in the proportion of one leucocyte to every 500 to 600 red cells. In man the corpuscles form

two-fifths to half of the total bulk of the blood, the exact volume in any sample being readily determined by centrifuging a little of it in a graduated capillary tube (*Hæmatocrit*) until the corpuscular layer shows no further shrinkage in bulk.

THE RED CORPUSCLES, when seen singly, are yellow in colour, but when massed together they give blood its red appearance. In man, and all animals except the camel tribe, they are circular, biconcave, non-nucleated discs, 8.8μ in diameter when fresh; in camels the corpuscles are oval and biconvex.

The number of red cells is diminished by hæmorrhage and in certain diseases, and is increased by living at high altitudes.

Each red corpuscle is soft, and alters its shape readily so that it can pass through even the narrowest capillary vessels. It is also elastic, and at once regains its shape when the compressing influence is removed. The peculiar shape of the mammalian corpuscle causes its surface to be some 20 per cent. greater than if it were spherical. It is now generally believed that the corpuscle is enclosed in an envelope consisting of lipoids containing the hæmoglobin in solution as a potassium salt in its interior. From the behaviour of the corpuscle in the presence of reagents, it is clear that this envelope behaves to some extent as a semi-permeable membrane, readily allowing the passage of water, but not of salts. Thus, if red blood-cells are placed in 0.9 per cent. sodium chloride solution, which is isotonic with mammalian blood-plasma, they are unaltered in appearance. But, if placed in a fluid the salt content of which is markedly below that of blood-plasma, water passes into the corpuscle by osmosis and distends or ruptures it, so that its hæmoglobin is discharged. On the contrary, if the surrounding fluid is hypertonic—for example, 2 per cent. NaCl—water passes out of the corpuscle, which in consequence becomes shrunken and crenated. The volume of the red cells is also increased by diffusion when the carbon dioxide content of the blood is increased. The cells of venous blood are therefore slightly larger than those of arterial blood.

THE WHITE BLOOD-CORPUSCLE is a colourless, nucleated cell, and several varieties occur in human blood. The most abundant type, about 70 per cent. of the leucocytes, is the *polymorphonuclear* (because its nucleus, which consists of lobes connected by fine strands, is variable in shape). This cell is about 10μ in diameter. It possesses the power of amœboid movement, and, because of its function of ingesting bacteria and foreign particles, is said to be “phagocytic.” Its protoplasm contains numerous fine granules which stain with neutral dyes, and are

described as *neutrophile*. Somewhat similar corpuscles in which, however, the nucleus is usually kidney-shaped, containing large granules which stain deeply with acid dyes, such as eosin, are called *eosinophile*; they form about 1 per cent. of the total number of leucocytes. A *basophile* variety in which the granules stain with such basic dyes as methylene blue, is found only occasionally in normal blood. *Small and large lymphocytes* form about 25 per cent. of the total number of leucocytes, the small variety being the more numerous. The large lymphocyte, or mono-nuclear, is phagocytic. Lymphocytes are distinguished by containing a large spherical nucleus surrounded by hyaline protoplasm, which does not contain granules.

The white corpuscles are increased in numbers in infections and in diseases of the bone marrow, etc.

A *differential count* of white blood-corpuscles is made by staining a film and counting the relative numbers of each variety of cell. The results are expressed as a percentage of the total number of white cells, but the total number of each kind per c.mm. of blood, which can be deduced from the total blood count and from the percentage, should also be given. Thus, in average blood :

	Red cells 5,000,000 per c.mm.	
	White cells 8000 to 10,000 per c.mm.	
Polymorphonuclears	6300 (70 %)	} 9000 per c.mm.
Lymphocytes	2250 (25 %)	
Other forms	360 (4 %)	
Eosinophiles	90 (1 %)	

PHAGOCYTOSIS.—The distinguishing feature of the polymorphonuclear leucocytes is their power of amœboid movement. The leucocytes are able to make their way through the capillary walls, and wander out into the tissue-fluids of the body. They are especially susceptible to certain chemical stimuli (*chemiotaxis*) and are found to concentrate in large numbers round various chemical substances placed in their neighbourhood. For example, they appear in force where pathogenic bacteria are active, and serve a useful purpose in surrounding and destroying these germs, thus constituting an important protective mechanism for the body (Fig. 22). When the

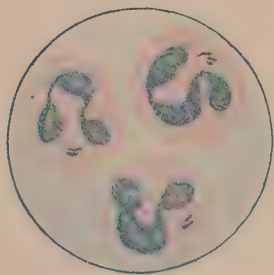


FIG. 22.—Phagocytosis. Three polymorphonuclear leucocytes, stained to show ingested bacteria. $\times 1500$.

leucocytes fail to overcome and ingest the bacteria, they may themselves be destroyed by the bacterial toxins. The same function of the removal of useless or harmful material is shown in other ways. For example, the removal of the tail of the tadpole is effected by leucocytes, and in the mammalian body dead cells and organic foreign substances, such as buried catgut ligatures, are ingested by the same cells. On account of this property of "eating up" bacteria and dead matter, polymorphonuclear leucocytes are included under the term *phagocytes*.

The leucocytes consist largely of proteins, namely cell-albumin, cell-globulin, and nucleo-protein; they also contain a little glycogen, some neutral fats, lecithin, and cholesterol. The inorganic salts which are most abundant in their composition are, as in the case of the red corpuscles, chlorides and phosphates of potassium.

In the embryo, leucocytes are derived from cells which resemble the erythroblasts but are colourless. In post-natal life the polymorphonuclear and eosinophile cells, as also the basophile cells, are derived from the special cells of red bone-marrow called *myelocytes*; the lymphocytes are derived from lymphatic glands and lymphoid tissue generally. The nuclear changes which accompany cell-division can be seen in definite areas, known as germ-centres, in the lymphoid tissue of the lymphatic glands and elsewhere.

The condition called *leucocytosis*, or increase of the number of leucocytes in the blood, occurs normally during the digestion of a protein meal. It also takes place in many infectious diseases, being accompanied by overgrowth of the red marrow, in which the polymorphonuclear cells are formed. The increase in the number of polymorphonuclear leucocytes in the blood is part of the process by which the body resists and overcomes infection by micro-organisms.

PLATELETS.—*Blood-platelets* are found in recently shed blood, and it is believed that they are a formed constituent of circulating blood, and not, as once supposed, a precipitate of nucleoprotein substances; their abundance varies with the coagulability of the blood, and they undoubtedly play an important part in determining clotting. Blood-platelets are colourless bodies, one-third to one-half the size of red corpuscles, and each contains a central group of granules resembling a nucleus.

HÆMOLYSIS.—The lipid envelope of the corpuscle is dissolved by weak alkalis, by ether, by bile-salts (which are solvents of fats), amyl-alcohol, soaps, higher fatty acids and saponin or

sapotoxin, setting free the hæmoglobin. The same result can be attained physically by alternately freezing and thawing blood. The setting free of the hæmoglobin by any of these means or by the addition of water or hypotonic salt solutions is called *hæmolysis*.

Certain physiological substances also bring about hæmolysis and have been termed *hæmolysins*. Snake-venom, and, in many cases, the serum from an animal of another species act in this way. Moreover, the serum of an animal A, which is not naturally hæmolytic for the blood of another animal B, may be made to become so if A has been inoculated with red cells from the species B some days before the experiment is made. Thus rabbit's red corpuscles are not normally affected by the serum of a guinea-pig. If, however, rabbit's blood has been previously injected into a guinea-pig, the serum from the latter will dissolve rabbit's red corpuscles.

The hæmolytic power of any serum depends upon the presence of two substances, one which is present in normal serum and is destroyed at a temperature of $55^{\circ}\text{C}.$, and is usually called *complement*; and a second which is stable at $55^{\circ}\text{C}.$, and may be produced in an animal by injection of the corpuscles of another animal, and is called *amboceptor*.

Hæmoglobin may thus be set free from the erythrocytes, and pass into solution in the surrounding fluid, in four ways:—

(1) By a physical process, *e.g.* by alternate freezing and thawing. (2) By chemical means; for example, by the solution of the lipoid stroma of the corpuscles by bile-salts. (3) By physiological agents, called hæmolysins. (4) By lowering the osmotic pressure: (See "Importance of Osmotic Pressure," Chapter I.)

As a result of hæmolysis by any of these methods the blood is said to be "laked." The hæmoglobin is in solution, and the blood, previously opaque on account of the reflection of light from the erythrocytes, becomes transparent.

AGGLUTINATION. BLOOD GROUPS.—When the blood of one individual is added to the serum of another, there is often an aggregation of the red corpuscles into clumps. This phenomenon, called *agglutination*, is an indication of incompatibility and is the precursor of hæmolysis. It is always seen if human blood is mixed with horse serum, and often when the blood of one person is mixed with the blood or serum of another person. In performing the operation of blood transfusion it is imperative that the *donor's corpuscles* be not agglutinated by the *recipient's plasma*, and this must be specifically tested. Human beings are divisible into four groups. In those of group I the serum agglutinates no other human corpuscles; this is the "universal recipient" group. The

serum of group II agglutinates corpuscles belonging to groups I and III; that of group III agglutinates corpuscles of groups I and II; group IV serum agglutinates corpuscles of all other groups, but group IV corpuscles are not agglutinated by any other group, so group IV is called the "universal donor" group. About 2 per cent. of individuals belong to group I, 40 to group II, 15 to group III, and 43 to group IV.

SECTION II

CHEMISTRY OF RED CELLS.—The red blood-corpuscles may be obtained in sufficient quantity for analysis by centrifuging blood and washing the deposit with 0.9 per cent. NaCl. They are found to consist of 63.3 per cent. of water and 36.7 per cent. of solids. The stroma is, therefore, as has already been pointed out, largely of a liquid nature. Hæmoglobin forms 95 per cent. of the dry solids, the remainder being made up of nucleoprotein, lecithin, cholesterol, fatty acid, and inorganic salts, the most abundant of the latter being potassium phosphate.

HÆMOGLOBIN is a compound of *globin* with an iron-containing substance, *hæmatin*; globin is a basic protein having the

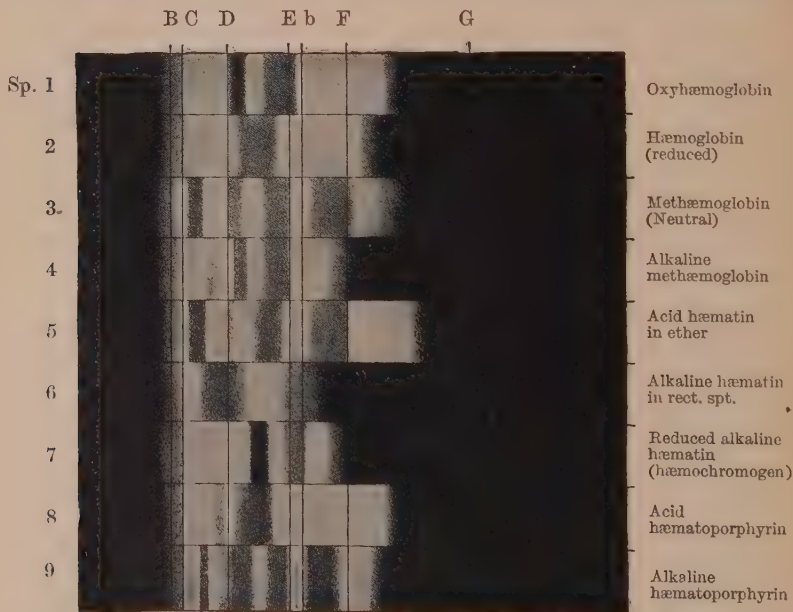


FIG. 23.—Spectra of hæmoglobin and its derivatives.
(From MacMunn's *Spectrum Analysis*.)

properties of a histone. The molecular weight of hæmoglobin is extremely large, probably of the order of 16,000. Each molecule contains one atom of iron. It is with this part of the molecule that the oxygen combines to form oxyhæmoglobin. Much experimental work has been done to ascertain whether the combination is a chemical or a physical one (*e.g.* adsorption). There is no doubt that it is of a chemical nature. Hæmoglobin is purple in colour, is soluble in water, and its solutions, when examined with the spectroscope, show a broad absorption-band in the green between Fraunhofer's lines D and E (Fig. 23, sp. 2).

OXYGEN - CARRYING POWER OF BLOOD.—

The most important property of hæmoglobin is its affinity for oxygen,

each molecule having power to combine with two atoms of oxygen to form oxyhæmoglobin. One gramme of hæmoglobin can combine with 1·34 c.c. of oxygen at N.T.P. The combination is a loose one, for the attached oxygen (dissociable oxygen) is given up if the solution containing the compound be exposed to a vacuum, or if a reducing agent, such as ammonium sulphide, be added to it, HbO_2 (oxyhæmoglobin) again becoming Hb (hæmoglobin). In the living body the same reduction takes place as the blood circulates through the capillaries of the tissues; as the blood flows through the lungs, hæmoglobin takes up oxygen and is converted into oxyhæmoglobin. In virtue of its power to combine with and give up oxygen, hæmoglobin acts as a carrier of oxygen from the lungs to the tissues. Oxyhæmoglobin has a characteristic scarlet colour, and its spectrum exhibits two absorption-bands in the green, between the D and E lines (Fig. 23, sp. 1).

Pure crystalline oxyhæmoglobin (Fig. 24) can readily be obtained in quantity as follows: horse blood is centrifuged, and the corpuscles very thoroughly washed with 0·9 per cent. NaCl solution. The paste of red corpuscles is then dialysed and the corpuscles thereby laked. After again centrifuging the laked corpuscles, in order to get rid of the stromata, the solution is

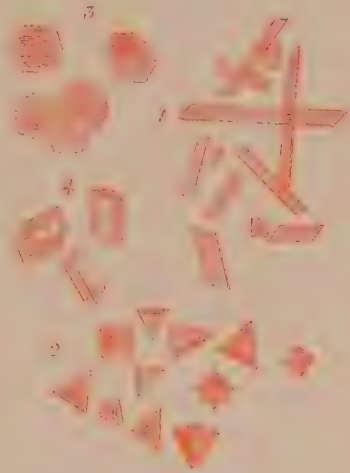


FIG. 24.—Oxyhæmoglobin crystals, magnified. (From Quain's *Anatomy*.)

1, from human blood; 2, from the guinea-pig; 3, squirrel; 4, hamster.

shaken with oxygen and cooled on ice, when an abundant crop of oxyhæmoglobin crystals separates out.

IMPORTANCE OF IRON IN BLOOD.—The oxygen-carrying power of hæmoglobin depends upon hæmatin, whose value in this respect is due to the presence of iron. The actual amount of iron in the blood is small. Hæmatin forms about 4 per cent. of the hæmoglobin molecule, and iron accounts for about 11 per cent. of the hæmatin, or about 0·06 per cent. of blood itself. Red corpuscles are continually being destroyed in the liver, by specialised cells called Kupffer cells, and the broken-down material is excreted to a large extent in the bile. Hæmatin appears in the bile in an iron-free form as bilirubin, the primary bile-pigment, the iron being retained by the liver-cells. The iron is eventually used in the formation of new erythrocytes in the red marrow.

CARBON MONOXIDE POISONING.—Hæmoglobin can also combine with some other gases; thus it combines with carbon monoxide to form a stable compound *carboxyhæmoglobin* (HbCO). The affinity of hæmoglobin for carbon monoxide is 300 times greater than for oxygen, so that, if blood is exposed to air containing 0·07 per cent. carbon monoxide (and 21 per cent. oxygen), half of its hæmoglobin enters into combination with carbon monoxide. A very small proportion of carbon monoxide in the air breathed will thus greatly diminish the oxygen-carrying power of hæmoglobin, upon which the life of the animal depends. Carboxyhæmoglobin differs slightly in colour from oxyhæmoglobin, strong solutions having a more florid appearance, and weak solutions retaining a pink colour, whereas the same dilution of oxyhæmoglobin has a yellow tint. Solutions of carboxyhæmoglobin, when examined spectroscopically, exhibit two bands in the green slightly nearer to the violet end than those presented by oxyhæmoglobin. This fact is made use of in the reversion spectroscope, by which the amount of carbon monoxide combined with hæmoglobin can be estimated. Carboxyhæmoglobin is unaffected by the addition of ammonium sulphide; but, if the solution containing it is exposed to a vacuum, carbon monoxide is evolved and reduced hæmoglobin is formed. Hæmoglobin forms a still more stable compound with nitric oxide, HbNO , but this is only of theoretical interest.

METHÆMOGLOBIN.—When a solution of oxyhæmoglobin is treated with potassium ferricyanide, a volume of oxygen is given off corresponding with the dissociable oxygen of the oxyhæmoglobin molecule, and the solution becomes brown, its

spectrum showing a characteristic band in the red in addition to other bands (Fig. 23, sp. 3). The brown substance is called *methæmoglobin*. When oxyhæmoglobin is treated with hydrazine hydrate, there is given off a volume of nitrogen corresponding with the volume of dissociable oxygen present in oxyhæmoglobin, as is indicated by the equation



On the contrary, when methæmoglobin is treated in a similar manner, its nitrogen yield is never more than half that of an equal weight of oxyhæmoglobin. It may be concluded that methæmoglobin contains only half as much reducible oxygen as oxyhæmoglobin, and that each molecule of methæmoglobin combines with only one atom of oxygen. Methæmoglobin is unaffected by exposure to a vacuum, but when ammonium sulphide is added to its solution, it is first converted into oxyhæmoglobin and is then rapidly reduced to hæmoglobin; shaking the solution with air then brings about the formation of oxyhæmoglobin. The formation of methæmoglobin, therefore, does not involve any disruption of the hæmoglobin molecule.

DECOMPOSITION PRODUCTS OF HÆMOGLOBIN.—If a solution of oxyhæmoglobin is warmed with weak acid or alkali, the globin is converted into metaprotein, and *hæmatin* is set free. Hæmatin is a dark brown amorphous substance, insoluble in water, soluble in acids or alkalies. In acid solution its spectrum shows, besides other absorption-bands, a characteristic band in the red (Fig. 23, sp. 5), nearer the red end of the spectrum than that given by methæmoglobin. The spectrum of the alkaline solution exhibits a rather faint band just to the red side of the D line (Fig. 23, sp. 6). On the addition of ammonium sulphide, alkaline hæmatin is converted into reduced alkaline hæmatin or *hæmochromogen*, the spectrum of which shows two absorption-bands in the green, some distance to the violet side of the D line, the band nearer D being the more distinct of the two (Fig. 23, sp. 7). As these bands can be seen in extremely dilute solutions, the formation of hæmochromogen constitutes a delicate spectroscopic test for blood-pigment.



FIG. 25.—Hæmin crystals, magnified. (Preyer.) (From Quain's *Anatomy*.)

As has already been said, hæmatin contains the iron of the hæmoglobin molecule. It forms a compound with hydrochloric acid, hydrochloride of hæmatin, or *hæmin*, which is easily obtained by heating blood with glacial acetic acid in the presence of sodium chloride. Hæmin occurs in dark brown rhombic crystals (Fig. 25), and its formation is utilised as a medico-legal test for blood. In the reduced condition, hæmatin will recombine with globin to form hæmoglobin, or a substance indistinguishable from hæmoglobin, provided the hæmatin has not been precipitated.

HÆMATOPORPHYRIN.—If hæmatin (or hæmoglobin) be treated with a strong mineral acid, iron-free hæmatin or *hæmatoporphyrin*, $C_{34}H_{38}N_4O_6$, is formed. Acid solutions of this substance show a spectrum with two absorption-bands, one on each side of the D line, that to the red side being the narrower (Fig. 23, sp. 8). The spectrum of alkaline solutions (Fig. 23, sp. 9) is somewhat similar to that of methæmoglobin. Hæmatoporphyrin occurs occasionally in the urine in sulphonal poisoning, its spectrum in such cases being of the alkaline type. Two similar substances are found in the body, *hæmatoidin* in old blood-clots, and *bilirubin*, the primary bile-pigment; they are formed from hæmoglobin and are said to be identical, each containing one atom less of oxygen than has hæmatoporphyrin. The proof that the capacity of hæmoglobin to combine with oxygen depends upon the presence of iron in its molecule is furnished by the fact that hæmochromogen, which contains iron, can take up and give off oxygen, whereas hæmatoporphyrin, which contains no iron, is unable to do so.

ESTIMATION OF HÆMOGLOBIN.—This estimation on blood is usually carried out by a colorimetric method. The apparatus used is called a *hæmoglobinometer* (Fig. 26) and consists of two tubes, one of which is sealed and contains a standard dilution of ox-blood, the hæmoglobin of which has been converted into carboxyhæmoglobin; the reason for this is that the colour of the standard solution is deeper and more permanent than one consisting of oxyhæmoglobin. A little distilled water is placed in the second tube, which is graduated; 20 c.mm. of blood are measured in a special pipette, and then discharged into the graduated tube. The blood, laked by the water, is exposed to coal-gas to convert the hæmoglobin into carboxyhæmoglobin. It is then diluted with distilled water till the tints of the two tubes are alike, and the level of the fluid in the graduated tube is read. If the latter is at the figure 100, the amount of hæmoglobin is said to be normal or “100 per cent.” If it is over 100, the blood is unusually rich in hæmoglobin; if the percentage

is below 100, the blood is deficient in hæmoglobin. The figure 100 per cent. represents blood of an *oxygen capacity* of 18·5 volumes per cent. (which corresponds to a *hæmoglobin* content of about 14 per cent.).

If the number of red corpuscles in the blood is ascertained at the same time, the value of the hæmoglobin content of each

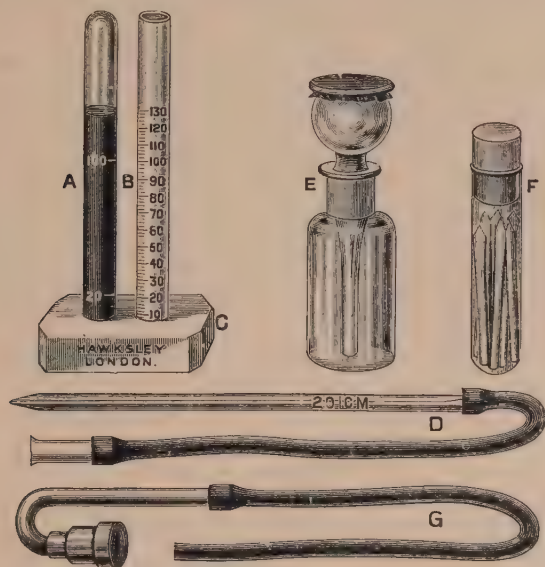


FIG. 26.—Hæmoglobinometer. (From Messrs. Hawksley.)

A, standard tube; B, graduated tube; C, stand; D, measuring pipette; E, distilled water bottle; F, needles; G, gas tube.

corpuscle can be stated. Thus, if the number of corpuscles is the normal five millions per cubic millimetre, and the hæmoglobinometer gives a reading of 50 per cent., each corpuscle contains only half the normal amount of hæmoglobin, *i.e.* the *colour index* is half the normal.

SECTION III

THE ORIGIN OF RED BLOOD-CORPUSCLES.—(1) *In early embryonic life* red blood-corpuscles are formed in areas, known as “blood-islands,” lying in the *area vasculosa* of the blastoderm. The blood-islands lie between the mesoderm and the endoderm, and are derived from the former. They consist of branched cells which unite to form a *synectium*. The nucleus of each cell divides and subdivides, each new nucleus becoming surrounded by protoplasm containing hæmoglobin. At the same

time a fluid, the plasma, appears between the nucleated fragments. The coloured cells thus formed are known as *erythroblasts*, and are the red corpuscles of the embryo. They multiply by mitotic division. *In later embryonic life* similar nucleated coloured cells, or erythroblasts, are formed from cells called hæmocyto blasts in the liver, and also in the pulp of the spleen. Non-nucleated erythrocytes, like those developed in post-natal life, are formed in the embryo in connective tissue. The connective-tissue cells become coloured by the formation of hæmoglobin, and the coloured protoplasm is subdivided into a number of discs, or erythrocytes, which lie free in the hollowed interior of the cell. Adjacent cells have meanwhile become united to form a syncytium, and the hollows become continuous along the connecting branches, so that a system of blood-vessels is formed.

(2) *In post-natal life* nucleated red corpuscles or erythroblasts are found in the red marrow of bone (Fig. 27). These are constantly undergoing mitotic division; the cells thus formed lose

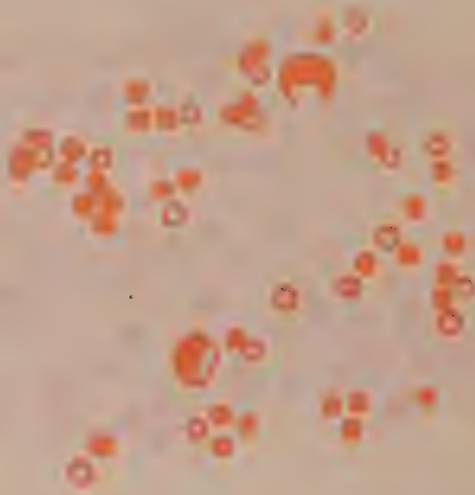


FIG. 27.—Red marrow of young rabbit. Magnified 450 diameters.

(From Schafer's *Essentials of Histology*.)

a, a, dividing myelocyte; *b*, polymorphonuclear leucocyte; *c, c*, erythroblast; *d*, erythrocyte; *f, f, f*, myelocyte; *g*, eosinophyl myelocyte; *h*, dividing erythroblast; *i*, giant-cell or megakaryocyte.

their nuclei by atrophy or extrusion, and pass into the blood-capillaries, which in the marrow probably have incomplete walls. Nucleated or immature (reticulated) red corpuscles may pass

into the blood-stream after birth in certain diseases in which a rapid destruction of blood-corpuscles is taking place.

THE FATE OF RED BLOOD-CORPUSCLES.—The duration of the existence of a single red corpuscle is not known, but there is evidence that large numbers of these cells are destroyed daily to form the pigment of the bile. Destruction occurs in health by two processes: (1) phagocytosis, which is effected by cells of reticulo-endothelial system, and (2) fragmentation. The Kupffer cells of the liver and the large endothelial cells of the spleen are examples of the reticulo-endothelial system. Moreover, the pigment of hair and that of the coloured parts of the skin is believed to be derived from hæmoglobin. Blood-corpuscles are also lost by accidental hæmorrhage, in disease, and, in the female, by menstruation. The deficiency brought about in all these ways, normal or abnormal, is as a rule rapidly and completely made good by the activity of the bone-marrow, which, in post-natal life, is the only source of the red corpuscles. When an unusually large and rapid formation of red corpuscles is required, for instance after severe hæmorrhage, the red marrow increases in amount, and replaces the yellow marrow to some extent.

SECTION IV

THE SPLEEN is a solid organ enclosed in a capsule, which consists partly of smooth muscle and partly of white fibrous tissue. The capsule sends trabeculæ, also containing unstriated muscle, into the interior of the organ; these branch to form a framework, in the interstices of which lies the splenic pulp. This consists of a fine meshwork of connective-tissue fibrils, covered at the nodes by endothelial cells, and containing in its spaces lymphocytes, red blood-corpuscles, and large reticulo-endothelial cells which are amœboid and often contain partly broken-down red corpuscles. Multinucleated giant-cells are also occasionally present.

The outer coat of the arteries in the spleen consists of lymphoid tissue, an enlargement of which is present on each arteriole and forms a Malpighian corpuscle. Some capillaries are found in the Malpighian bodies, but, with this exception, the arteries open directly into the splenic pulp, from which the blood is again gathered up to leave the spleen in the splenic vein. The blood thus comes into direct contact with the tissue-elements of the spleen, whereas in almost every other organ of the body it is separated from the tissues by a capillary wall.

The flow of blood through the spleen is assisted by the alternate contraction and relaxation of the muscular tissue in its capsule and trabeculæ; this rhythmic contraction, which takes place about once a minute, can be recorded by enclosing the spleen in a plethysmograph connected with a tambour. The muscular fibres are supplied with nerves from the sympathetic system, and the direct or reflex stimulation of these nerves, or the injection of adrenaline, produces contraction of the muscle and diminution of the volume of the spleen.

THE FUNCTIONS OF THE SPLEEN.—These are: (1) blood storage; (2) blood destruction; (3) blood formation; (4) iron storage; (5) lipid storage; (6) antibody formation; and (7) uric acid formation.

(1) *Blood storage.*—The meshes of the spleen are full of red blood-corpuscles. Severe exercise, hæmorrhage, carbon monoxide poisoning, or oxygen want cause the spleen to contract. The stored corpuscles enter the circulation (Barcroft). The number of circulating corpuscles may thus be increased by more than 10 per cent.

(2) *Blood destruction.*—This has already been referred to above. There is no doubt that the spleen forms an important part of the reticulo-endothelial system.

(3) *Blood formation.*—During life the lymphoid tissue in the spleen is actively engaged in the formation of lymphocytes. It thus aids the lymph glands. During fœtal life the spleen like the liver is also engaged in the formation of red blood-corpuscles. This function may be resumed if during the post-natal life severe hæmorrhage or some other condition greatly depletes the number of red blood-corpuscles in the circulation.

(4) *Iron storage.*—The spleen stores iron, like the liver cells. The importance of this lies in the fact that iron is essential for the formation of new hæmoglobin and that diets are very variable in the amount of iron they contain.

(5) *Lipoid storage.*—The lipoids, cholesterol and lecithin, are stored in the spleen, possibly from the disintegration of the envelopes of the red blood-corpuscles.

(6) *Antibody formation.*—Not only do the spleen cells produce antibodies to the toxins of bacteria, *e.g.* diphtheria, tetanus, etc., but they also attack bacteria and parasites which have gained entrance to the blood-stream. The free communication between the blood and the spleen pulp is specially important in this connection.

(7) *Uric acid formation.*—It can be shown by experiment that the spleen contains the enzymes xanthinase and hypoxanthinase,

which convert xanthine and hypoxanthine respectively into uric acid.

SECTION V

THE BLOOD-PLASMA.—When blood is shed it rapidly becomes viscid, and in a few minutes sets to form a clot. It is therefore necessary to use means to retard or prevent clotting in order to obtain plasma for examination and analysis. The various methods which are used for this purpose will be described in connection with coagulation.

Plasma is a pale yellow fluid, and has a specific gravity of about 1030, this being considerably lower than that of blood as a whole. The red corpuscles have a specific gravity of about 1090, and therefore sink if blood which is prevented from coagulating is allowed to stand. The velocity of sedimentation is greatly accelerated when agglutination occurs.

On analysis, plasma is found to contain a large number of substances, some of which, particularly fibrinogen, appear to be essential constituents of the plasma itself, some are foodstuffs being conveyed to the tissues, some are waste products being carried to excretory organs, and others are hormones, enzymes, and bodies of like nature. A list of the principal constituents will now be given.

CHEMISTRY OF THE BLOOD—

Water, 91 to 93 per cent.

Proteins—serum-albumin, serum-globulin, fibrinogen—6 to 8 per cent.

Glucose, 0·08 to 0·15 per cent.

Neutral fats, lecithin, and cholesterol.

Urea (0·02 to 0·05 per cent.), amino-acids, urates.

Inorganic salts—chlorides, sulphates, phosphates, and bicarbonates of sodium, potassium, calcium, magnesium, and iron. The most abundant salts are sodium chloride and bicarbonate, in contradistinction to the red cells and the tissues, in which the chief salts are mono- and di-potassium phosphate and potassium chloride.

Two yellow pigments, *Carotin* ($C_{40}H_{56}$) and *Xanthophyll* ($C_{40}H_{56}O_2$), both of which are derived from the food. Traces of *bilirubin* also occur.

Gases in solution—oxygen, carbon dioxide, and nitrogen.

THE PROTEINS OF PLASMA.—If an equal volume of a saturated solution of sodium chloride be added to plasma, and the

mixture be allowed to stand, a sticky white precipitate separates out, consisting of *fibrinogen*. This substance is a globulin, and the precipitate may be dissolved in weak salt solutions. Fibrinogen exists in much smaller quantities than the other proteins, forming about 0·3 per cent. of the plasma. If plasma be allowed to clot, a comparatively insoluble, stringy substance, called *fibrin*, is formed, and, if this be removed, the fluid which remains is plasma minus fibrinogen, and is called *serum*.

When serum is treated with an equal volume of a saturated solution of ammonium sulphate, a precipitate of *serum-globulin* is obtained. This precipitate is found to be a mixture of two substances, one of which, euglobulin, is a true globulin, while the other, pseudo-globulin, resembles albumin in being soluble in distilled water. If serum from which serum-globulin has been removed is saturated with ammonium sulphate, a precipitate of *serum-albumin* is obtained. The filtrate from this contains no other protein. Fibrinogen coagulates at about 56° C., serum-globulin at 75°, and serum-albumin at a slightly higher temperature.

Although these proteins can be separated from serum by chemical methods, there is reason to believe that in the serum itself these substances are combined to form one—*serum-protein*.

THE OSMOTIC PRESSURE OF BLOOD-PLASMA.—The osmotic pressure of the plasma is the same as that of the corpuscles. The proteins of plasma have a slight osmotic pressure, but the osmotic pressure of plasma is chiefly due to its inorganic salts. One method of ascertaining the osmotic pressure of a fluid is to determine its freezing-point; in the case of blood this is found to be *minus* 0·56° C.

When, *e.g.* after injecting a concentrated salt solution into the blood-stream, the osmotic pressure of the blood becomes higher than that of the tissues, water will pass from the tissues into the blood in the capillaries, and salts will diffuse from the blood into the tissues. If the osmotic pressure of the blood becomes lower than that of the tissues, as happens when water or hypotonic salt solutions are injected, the reverse processes will occur, water passing from blood to tissues and salts from tissues to blood. This interchange is an important factor in the maintenance of the balance between the intake and output of water and salts. The readjustment of the blood to the normal osmotic pressure occurs with great rapidity whenever it is disturbed. After injecting strong sodium sulphate solution sufficient to double the osmotic pressure of the blood, measurement shows

that the normal osmotic pressure is restored in a few minutes, although the *composition* of the plasma is still abnormal, since it contains increased sulphate and diminished chloride.

PROTECTIVE SUBSTANCES IN THE PLASMA.—A large number of substances, when introduced under the skin or directly into the circulation (but not when given by the mouth), give rise to the formation by the tissues, and the setting free in the blood-stream, of products which tend to destroy or to precipitate the substance introduced, or to neutralise its action. The products thus formed are called *antibodies*, those which excite their formation being called *antigens*. The most important, if not the only antigens are proteins, including harmless bodies such as egg-white and caseinogen. Crystalloid substances of small molecular weight seem unable to give rise to antibodies.

If a little *human* blood-serum is injected into a rabbit on several occasions at intervals of a week, the blood-serum of the rabbit acquires the power, when tested *in vitro*, of precipitating the proteins of *human* serum, but not those of the serum of other animals. The substance thus formed in the rabbit's blood is called a *precipitin*. If another rabbit is injected with *sheep's* serum, the precipitin formed will precipitate *sheep's* serum *in vitro*, but not that of any other animal. The precipitin acts, therefore, only on the serum of an animal of the same species as that from which blood is taken for injection into the rabbit. For this reason the reaction is said to be *specific*. Since this reaction is not only one of the most delicate known tests for the presence of blood, but also makes it possible to ascertain the species of animal from which the blood was derived, it has been used in medico-legal cases to ascertain whether blood, for example, on clothes or weapons, is of human origin or not.

Again, when poisons (toxins) formed by bacteria are introduced into the body, antibodies are formed which neutralise the toxin. If, for example, a minute amount of diphtheria-toxin is injected at intervals into an animal, the latter forms *antitoxin* in considerable amount. This antitoxin is able to neutralise diphtheria-toxin, and such an animal will now survive the injection of a dose of toxin many times larger than that which would previously have killed it; and it is said to be *immune* to that toxin. In this example the toxin and antitoxin combine directly with one another. In other cases, however, the antibody which is formed does not itself destroy the antigen, but forms a link between the antigen and a substance present in normal serum and known as *complement*; the complement, thus linked on to the antigen, is able to destroy it. Antigens of this kind include

bacteria, red blood-corpuscles and tissue-cells, and the antibodies are called *lysins*. The formation of *hæmolysin* (p. 58) is an example of this process.

The capacity to form antibodies, which can destroy or neutralise bacteria and their toxins, is one of the fundamental means by which human beings are enabled to resist, or to recover from, diseases of bacterial origin.

ANAPHYLAXIS.—If a small dose of an antigen, such as egg-white, is injected into an animal, and, after an interval of sixteen days or more, a second, even smaller, dose is given, the animal becomes extremely ill, and may die in a few minutes. In guinea-pigs, which are particularly sensitive, there is a marked fall of blood-pressure, extreme constriction of the bronchioles, and convulsions. In the dog vomiting and sanguineous diarrhœa, with fall of blood-pressure, intense itching of the skin, ataxia, and dyspnœa are the chief symptoms. In man the symptoms are similar, the milder forms being confined to skin irritation and rashes. This hypersensitiveness of an animal to a second dose of an antigen is known as *anaphylaxis*.

In the state of anaphylactic shock there are decided changes in the blood; its coagulability is reduced, the number of leucocytes is increased (dog and rabbit) or diminished (guinea-pig), and the number of platelets is considerably reduced.

If the animal recovers from the anaphylactic shock, it is found to be insensitive to further doses of antigen until after the lapse of some considerable time. It is said to have been *desensitised*. If the serum of a sensitive (anaphylactic) animal be injected into a normal animal the latter also becomes anaphylactic (*i.e.* sensitive to the antigen) even though it has not received a sensitising dose of antigen: this phenomenon is called *passive anaphylaxis*. Allied to this is the fact that if a sensitised female becomes pregnant, the offspring inherit the anaphylactic condition.

It is probable that anaphylaxis represents a late phase of immunisation in which the "precipitins," previously circulating in the blood-plasma, have become absorbed by the tissues which are thereby rendered sensitive to the antigen.

SECTION VI

THE REACTION OF THE BLOOD.—As pointed out in Chapter I, every aqueous solution contains free hydrogen (H) ions and hydroxyl (OH) ions, and its reaction depends upon the proportion of these two ions to one another. In a perfectly neutral solution the two kinds of ion are present in equal amount, whereas

if the hydrogen ions are in excess, the solution is acid, and if the OH ions are the more numerous, it is alkaline. In blood the OH ions are in excess, and it has a P_H of 7.4.

THE RESTORATION OF THE NORMAL REACTION.—This, as already mentioned in Chapter I, is effected temporarily by excretion of increased amounts of CO_2 by the lungs; more permanently by the excretion, as required, of either alkaline or acid salts by the kidney. When excess acid has to be dealt with, ammonia salts of the acid are excreted by the kidney. Further details of the latter will be given in Chapter XXI, on the Kidney.

THE BUFFERING OF THE BLOOD.—A considerable amount of a fixed acid can be added to blood without producing more than a trivial change in its reaction. The reason is that the acid reacts with sodium bicarbonate to form a neutral salt, setting free carbon dioxide which undergoes so little ionic dissociation that the H ion concentration of the blood increases very slightly. Hence the presence of sodium bicarbonate in the plasma helps to prevent the reaction of the blood from altering to such an extent as to become injurious to the organism.

The sodium bicarbonate of the plasma thus acts as a *buffer* substance. The reaction of whole blood is much more stable than that of separated plasma, *i.e.* it is better buffered. The additional buffering provided by the corpuscles is called *secondary buffering* and is due to an interaction between corpuscles and plasma, whereby the bicarbonate content of the plasma is raised when carbon dioxide is added to, and lowered when it is removed from, the blood (see p. 183).

DETERMINATION OF THE REACTION OF THE BLOOD.—The simplest method is the indicator method, which depends on the principle that certain coloured indicators, such as neutral red or phenol red, show a characteristic tint at each particular H ion concentration. The method further depends on the fact that moderate dilution of the plasma by dialysis does not alter its reaction. A collodion sac holding 2 to 3 c.cm. is completely filled with the (oxalated) blood, and allowed to dialyse into 1 c.cm. of 0.8 per cent. sodium chloride solution, contained in a flat-bottomed tube, contact of both blood and dialysate with the air being reduced to a minimum by an air-tight cap. In this way a dialysate is obtained, in which the ratio of free to fixed carbon dioxide is the same as in the blood-plasma. After twenty minutes' dialysis, neutral red or phenol red is added in measured amount to the clear and colourless dialysate, contact of which with the atmosphere is

then prevented by pouring a layer of liquid paraffin on to its surface. The vessel containing the dialysate is then placed in a comparator box, together with a similar vessel in which a mixture of standard phosphate solutions also containing indicator, is made in known proportions, until the tint of the fluid exactly matches that of the dialysate. By reference to a specially constructed graph the reaction of the resultant mixture is at once ascertained, and is the same as that of the blood. (Dale and Evans.)

THE GLASS ELECTRODE METHOD.—Another method of measuring the reaction of the blood is the glass electrode technique (Kerridge). Briefly, the apparatus consists of a very thin glass cup. Inside this cup is placed the blood to be examined, and on the outside standard buffer solution of known P_H . Suitable non-polarisable electrodes are placed in contact with both blood and solution and the potential between them carefully measured by an electrometer, when the H ion concentration of the blood can be ascertained from a chart. The great advantage of the method is that the P_H of whole blood can be quickly and accurately determined. The loss of CO_2 is avoided and errors are not introduced by the oxygen combined with the hæmoglobin.

SECTION VII

THE COAGULATION OF THE BLOOD.—When blood is shed, it begins to set into a jelly-like clot within three to ten minutes. The clot gradually contracts, expressing a yellow fluid, the serum, as it does so; and within ten to forty-eight hours the process results in a shrunken, firm clot floating in the expressed serum.

If a drop of blood be placed on a slide and covered with a cover-slip, the process of clotting may be observed microscopically. It is found that the red corpuscles become aggregated into rouleaux, and that between the aggregations delicate threads of fibrin make their appearance. Clotting thus consists in the formation of a meshwork of threads of fibrin, entangling the corpuscles; and the subsequent shrinking of the clot is due to the contraction of the newly formed fibrin.

FIBRIN may be obtained in quantity by whipping a large volume of freshly shed blood with a bundle of twigs, to which it adheres as it is formed. Blood treated in this way has really clotted. It consists of corpuscles suspended in serum, and is spoken of as *defibrinated blood*. The fibrin, when freed from blood-pigment by washing, is a white, stringy, elastic substance. It is

insoluble in water and in dilute salt solutions, but dissolves slowly in 5 per cent. sodium chloride. It swells up and slowly dissolves in 0·2 or 0·4 per cent. hydrochloric acid, with the formation of acid metaprotein.

If the clotting of blood be delayed or prevented by one of the methods described later (p. 78), and the blood be centrifuged, the corpuscles will settle at the bottom of the vessel, and the supernatant plasma can be poured off. If fibrinogen, precipitated from the plasma by the method described on p. 70, is dissolved in a weak NaCl solution, it usually clots, fibrin being formed.

The essential change in the coagulation of blood is therefore the conversion of fibrinogen into fibrin. The former substance is no longer present in defibrinated blood or serum. The process of clotting may be represented diagrammatically in this way :—

Plasma = Serum + Fibrin.

Fibrin + Corpuscles = Clot.

THROMBIN.—When fibrinogen is freed from other substances it is found to have lost the property of spontaneous coagulation. If, however, some blood-serum is added to such a pure solution, clotting will occur. It is clear, therefore, that at least two substances are necessary for the formation of fibrin, and that one of these is contained in blood-serum. If twenty volumes of alcohol are added to one volume of serum, a precipitate of serum-proteins is formed, which after some weeks becomes insoluble in water. If this precipitate be then dried and extracted with water, the solution so obtained will, if added to a solution of fibrinogen, cause the latter to clot. The watery extract contains a substance of unknown composition, which has been called *thrombin*.

We therefore find that the formation of fibrin is due to the interaction of fibrinogen and thrombin, and it has been shown that a combination of the two bodies takes place, because, if excess of fibrinogen be present, the amount of fibrin formed is proportional to the amount of thrombin added to it. Moreover, if fibrin is treated for some time with 8 per cent. sodium chloride solution, thrombin is dissolved out.

For many years thrombin was believed to belong to the group of ferments, but it has been shown (1) that it is not destroyed by boiling, and (2) that the amount of fibrin formed is in proportion to the amount of thrombin present. It is characteristic of a ferment that, if the products of its activity be removed, it will in time act upon all the substrate which is present. Thrombin, however, is used up in the formation of fibrin, so that if there is an

excess of fibrinogen the surplus remains unchanged, unless fresh thrombin is added.

THROMBOGEN (OR PROTHROMBIN).—Thrombin itself is not contained in the blood-stream of the living animal. If blood is drawn directly from a blood-vessel into alcohol, it contains no thrombin, so that the latter body must be produced after the blood is shed. It has, in fact, been shown that it is derived from a precursor, which has been called *thrombogen*, by the combination of the latter substance with calcium salts. If freshly shed blood is mixed with potassium oxalate solution in such quantity that the mixture contains 0·1 per cent. of potassium oxalate, the calcium salts of the plasma are precipitated as calcium oxalate, and the blood will not clot. The subsequent addition of calcium chloride is followed by coagulation. If, however, a solution of thrombin free from calcium is mixed with “oxalated” blood, clotting will take place, although no calcium is present. The presence of calcium is essential, therefore, to the formation of thrombin, but the thrombin, when once formed, will cause blood to clot, even when calcium salts are absent.

CEPHALIN.—The formation of thrombin from thrombogen and calcium salts is brought about, or at least facilitated, by an activating substance which used to be called *thrombokinase*. Now, however, it is known to be a phospholipine related to lecithin. The name *cephalin* has now been given to it (Howell). This is derived in mammals mainly from the blood-platelets. If “oxalate plasma” from a mammal is allowed to stand for two or three days on ice, a precipitate of platelets collects at the bottom of the vessel. The plasma still contains thrombogen, but will no longer coagulate on the addition of lime salts. It will clot, however, if some of the precipitated platelets, or an extract of an animal tissue, be added to it along with the lime salts, the extra factor, obtained from the platelets or tissue, being cephalin. The blood of birds will not clot if it is drawn directly from a blood-vessel without contact with the tissues. If, however, it is allowed to flow over the adjacent tissues in its passage from the vessel, or if a little tissue-extract is added to it, it will coagulate readily. Cephalin is therefore present in nearly all the tissues of the body as well as in the platelets, and this wide distribution facilitates the protective clotting of the blood which takes place on wounded surfaces. The leucocytes have also been supposed to discharge cephalin when blood is shed.

The factors concerned in coagulation may be diagrammatically summarised as follows :—

Thrombogen (or Prothrombin) + Cephalin
+ Ca Salts = Thrombin.
Thrombin + Fibrinogen = Fibrin.
Fibrin + Corpuscles = Clot.

HEPARIN.—Blood does not clot in the vessels, and this must be due to one of two reasons: either an essential factor for coagulation is not present, or clotting is prevented by some agent which inhibits the process. With regard to the former possibility, fibrinogen exists in normal blood, calcium salts are undoubtedly present, and thrombogen must be a constituent of the blood in some form. There is good ground for believing that the circulating blood contains little or no cephalin. As regards the second possibility, evidence shows that a substance, *heparin*, is a normal constituent of blood, and that it is formed in the liver. It is stated, for example, that the injection of cephalin or of thrombin into a blood-vessel results in the production of such an antibody, so that the blood becomes deficient in coagulating power, just as a precipitin is produced as a result of the injection of foreign protein. Hence it has been inferred that small quantities of thrombin are continually being produced in the blood, being also set free by the breaking down of white blood-corpuscles and of the tissues generally. The presence of thrombin leads to the formation of heparin in the liver, and in this way clotting in the blood-vessels is prevented.

CONDITIONS WHICH ACCELERATE CLOTTING.—The rate of coagulation is accelerated (1) by a certain degree of warmth, (2) by agitation of the blood, and (3) by increasing the extent of the foreign surface with which the blood is in contact. A practical application of the latter fact may be made by applying a sponge or cotton-wool to a bleeding surface to aid in the arrest of hæmorrhage. It is probable that the foreign surface facilitates the formation and disintegration of platelets, with consequent increased production of thrombokinase.

INTRAVASCULAR CLOTTING.—The rapid injection into the blood-stream of an animal of a quantity of a saline extract of a cellular organ, such as the thymus or a lymph-gland, leads to the coagulation of the blood throughout the whole vascular system. This result is generally ascribed to the presence of cephalin in the extract. Small quantities of a similar extract, if slowly injected, have an opposite effect, rendering the blood incoagulable. The difference in the results, according to the quantity of extract injected, has not been satisfactorily explained. Intravascular

clotting is also produced by the injection of the venom of certain snakes, but not by moderate quantities of thrombin. Local clotting may be produced by the injection of strong quinine solutions. Thus varicose veins may be occluded by it. It appears to damage the lining of the lumen of the vein, liberates cephalin locally, and the blood on coming into contact with the damaged vessel, will at once clot.

CONDITIONS WHICH RETARD OR PREVENT CLOTTING.—

These may be classified as: (1) Prevention of contact with a foreign surface. (2) Removal of one or more of the substances concerned in the formation of fibrin. (3) Interference with the interaction of the substances concerned in the formation of fibrin. (4) The use of antithrombin. (5) Hæmophilia.

(1) Coagulation is delayed if blood is shed into a vessel the interior of which is smeared with grease of any kind. It is delayed for a longer time if the blood is kept in contact with the lining of a blood-vessel. If a large vein containing blood is ligatured in two places and the ligatured portion is excised, the blood in the vein may remain fluid for days.

(2) (a) Calcium salts are precipitated by the addition of potassium oxalate or of sodium fluoride to blood. (b) Sodium fluoride precipitates not only calcium but also thrombogen, so that fluoride blood will not clot on the subsequent addition of lime salts. (c) Sodium citrate may also be used to prevent coagulation. It forms with calcium a salt in which the calcium is not ionised. Calcium will not combine with thrombogen unless it is in the ionised condition. (d) If one volume of a saturated solution of magnesium sulphate be added to three volumes of blood, and the mixture be allowed to stand for twenty-four hours, the thrombokinase and thrombogen are precipitated and clotting will not take place on dilution. For the first few hours after the addition of the sulphate the clotting is merely retarded by the excess of salt, and the blood will clot if it is diluted.

(3) (a) Coagulation may be prevented by cooling freshly shed blood to 0°C . (b) The addition to the blood of an equal volume of saturated solution of sodium sulphate will prevent or delay clotting, but coagulation will take place when the mixture is diluted, showing that the action of the salt is purely mechanical. (c) Plasma is said to lose the power of coagulation when it is deprived of its lipoid constituents.

(4) Hirudin, a substance obtained from extracts from heads of leeches, is an antithrombin, and will prevent clotting either if added to shed blood or if previously injected into a blood-vessel. The injection of peptone will render blood incoagulable, and such

blood, when added to blood shed in the ordinary way, will prevent coagulation of the latter; but peptone itself has no retarding effect on coagulation when added to shed blood. From experiments such as these it is clear that peptone has no direct action in preventing coagulation, but that it leads to the production of heparin, which is discharged into the circulating blood.

(5) *Hæmophilia* is a disease passed by a mother in whom it is latent to her sons who are affected by it. Her daughters, who are not affected, but in whom it is latent, pass it to their sons who are affected and to their daughters who pass it in the same way to their children. Bleeding is checked with great difficulty, even from small cuts, because the time required for coagulation is greatly increased. The condition appears to be due to defective cephalin formation.

SECTION VIII

THE TOTAL QUANTITY OF BLOOD IN THE BODY.—The amount of blood in the body of an animal may be ascertained in the following way. A small sample of the animal's blood is first taken, diluted 100 times with distilled water, and kept as a standard of comparison. The animal is then bled, and the blood-vessels are washed out with saline solution. Finally the animal is minced, and the tissues are extracted with distilled water to remove any remaining blood. The blood, saline washings, and watery extracts are mixed, and a sample of the mixture is diluted till it is of the same tint as the standard sample. The amount of dilution being known, the total amount of blood can be calculated. Two experiments of this kind have been performed on the bodies of guillotined criminals, and from these it was found that the blood in man forms one-thirteenth of the weight of the body.

CARBON MONOXIDE METHOD.—Haldane has devised a method for ascertaining the quantity of blood in the living subject. This method is based upon the affinity of hæmoglobin for carbon monoxide. A small quantity of blood is withdrawn, and its oxygen capacity, that is, the amount of oxygen with which it will combine, is estimated. The subject is then allowed to breathe air containing a known amount of carbon monoxide, say 120 c.c., which is all absorbed by the blood, forming carboxyhæmoglobin. A small quantity of blood is again withdrawn, and the proportion of its hæmoglobin which is combined with carbon monoxide is estimated by a suitable method. If one-sixth of the hæmoglobin is combined with carbon monoxide, and 100 c.c. of blood were shown to be capable of combining with 18 c.c. of oxygen, then,

since carbon monoxide replaces an equal volume of oxygen, 100 c.c. of blood have taken up 3 c.c. of CO. The total volume of blood must thus be $100 \times \frac{120}{3} = 4000$ c.c. By this method the total blood has been calculated to be approximately one-fifteenth of the weight of the body.

VITAL RED METHOD.—Another method of measuring the volume of the blood has recently been introduced and is applicable to man. It consists essentially in injecting into the circulation a known amount of a dye, the one usually employed being *vital red*. After waiting three minutes to allow the dye to become uniformly distributed in the plasma, a sample of blood is withdrawn from a vein and centrifuged. The plasma is coloured red by the dye, and its depth of colour is matched against that of a known dilution of the dye in saline solution. Another sample of the individual's blood is centrifuged in a graduated tube in order to ascertain the relative amount of plasma and corpuscles in the blood. From these data the volume of the blood can be determined. If, for example, 1 c.c. of a 1 per cent. solution of the dye is injected, and the plasma, when subsequently withdrawn, matches in colour a 0.001 per cent. solution of the dye, the dye injected into the blood has been diluted 1000 times by the plasma; hence the volume of the plasma is 1000 c.c., and, if the plasma is found to form 50 per cent. of the blood, the total volume of the blood is 2 litres.

Results obtained by this method indicate that the blood forms approximately one-thirteenth of the body-weight, being on an average $5\frac{1}{2}$ to 6 kilograms. In health the volume is very constant, although it is said to be increased during pregnancy and also in individuals living at high altitudes.

CHAPTER V

THE HEART

SECTION I

ANATOMY OF THE HEART.—The life of the muscles, of the nervous system, and of every tissue of the body, depends upon their receiving an adequate supply of food and oxygen ; and one of the most important functions of the blood is to convey oxygen and nutritive material to the tissues, and to carry away carbon dioxide and waste products which are formed by the tissues. In order that this function may be carried out, the heart and blood-vessels furnish the mechanism by which a constant circulation of the blood throughout the body is maintained ; and, by means of the central nervous system, the activities of this mechanism can be varied in response to the ever-changing needs, either of the body as a whole, or of its different parts.

The heart acts as a pump, and drives the blood along the arteries, through the capillaries and veins, and back to the heart. The actual interchange of nutritive material and waste products between the blood and tissues takes place solely through the walls of the capillaries, and the entire circulatory mechanism is adapted to maintain the conditions favourable to this interchange.

The heart is a hollow muscular organ lying in the thorax between the lungs, and slightly to the left of the middle line of the body. It is conical in shape, the apex being directed downwards and to the left, and is divided by a septum into right and left halves, which do not communicate directly with each other. Each half consists of two chambers, an upper thin-walled auricle (atrium) and a lower thick-walled ventricle. Into the right auricle open the superior vena cava, bringing blood from the head and upper limbs, the inferior vena cava, conveying blood from the rest of the body, and the coronary sinus, conveying blood from the muscular substance of the heart itself. The right auricle opens into the right ventricle by an orifice guarded by a valve known as the tricuspid valve ; this consists of three triangular cusps, arising from the fibrous junction between the

auricle and ventricle and hanging down into the ventricle. The cusps consist of connective and elastic tissue, and are so arranged as to permit the flow of blood from auricle to ventricle, but not in the reverse direction. From each cusp a number of tendinous threads, *chordæ tendineæ*, pass to be attached to projections of the ventricular wall, known as the papillary muscles.

THE VENTRICLES.—The right ventricle possesses two openings: (1) the auriculo-ventricular just described, and (2) the opening into the pulmonary artery, which conveys blood from the heart to the lungs. The latter opening is provided with a valve having three semilunar cusps composed of strong fibrous and elastic tissue. In the centre of the free border of each cusp is a small fibrous nodule, the *corpus Arantii*, which serves to strengthen the valve. When the valve is closed, the free borders of the cusps come into contact with each other and are pressed together, thereby preventing the return of blood from the pulmonary artery to the ventricle.

The general arrangement of the left side of the heart is very similar to that of the right side. Two pulmonary veins from each lung open into the left auricle. The auriculo-ventricular valve possesses only two cusps; it somewhat resembles a bishop's mitre, and is known as the mitral valve. The cusps, like those of the right auriculo-ventricular valve, are connected by tendinous cords with the papillary muscles and with the wall of the left ventricle. Opening out of the left ventricle is the aorta, which is provided with a valve having three semilunar cusps similar in structure to those of the pulmonary artery.

The cavities of the heart are lined by a smooth membrane, the *endocardium*, composed of delicate connective and elastic tissue covered by flattened endothelial cells.

THE HEART-MUSCLE.—The substance of the heart, *myocardium*, consists of muscular tissue bound together by connective tissue and supplied with blood from the coronary arteries. The muscle is arranged in sheets composed of fibres, which are built up of short cylindrical segments or cells; each cell has an oval nucleus and shows an indistinct longitudinal and transverse striation. The fibres are branched, the branches of adjacent fibres uniting with one another, so that the heart-muscle forms a continuous network of cells, known as a *syncytium*.

The wall of the auricles is composed of (a) superficial fibres common to both auricles, and (b) deep fibres, both looped and annular, proper to each auricle; the annular fibres form muscular rings around the openings of the great veins. The auricles are

joined to the ventricles by strong fibrous rings, which encircle the auriculo-ventricular orifices, and by a band of modified muscular tissue, known as the *auriculo-ventricular bundle*, the importance of which will be considered later.

The muscular fibres of the ventricles are arranged in a very complex manner. From the fibrous rings, which unite the auricles and ventricles, a superficial stratum runs in a spiral direction to the apex of the heart; here the fibres form a whorl and then ascend in the inter-ventricular septum and on the inner surfaces of the ventricles, to end in the papillary muscles. Between the layers thus formed are deeper, transverse fibres, most of which are arranged in an *∞*-shaped manner, springing from the papillary muscles of one ventricle and ending in the papillary muscles of the other ventricle; they are united by muscular strands with the layers of the superficial stratum. The muscle is so arranged that, when contraction occurs, the cavities of the ventricles become smaller.

The wall of the left ventricle, which drives the blood through the greater part of the body, is approximately three times as thick as that of the right ventricle, which drives the blood only through the lungs; the thin-walled auricles merely discharge their contents into the relaxed ventricles. The capacity of the two ventricles is approximately the same, amounting in each case to a maximum of 140 to 200 c.c. in man, and it is rather greater than that of the auricles.

THE PERICARDIUM is a fibrous sac enclosing the heart, attached below to the diaphragm and lined by flattened cells. The epithelial layer is reflected where the great vessels pass through it and covers the surface of the heart (*epicardium*). The inner wall of the sac is smooth and is moistened by a little lymph (pericardial fluid), so that the movements of the heart are carried out with hardly any friction. The pericardium also serves to prevent over-distension of the heart when it is being filled by the inflow of blood from the veins.

THE BLOOD-VESSELS.—The *arteries*, which convey blood from the heart to the capillaries, are thick-walled tubes made up of muscular and elastic tissue. A medium-sized artery shows three coats—outer, middle, and inner. The outer coat is composed of fibrous tissue. The middle coat consists of smooth muscle-fibres and of yellow elastic fibres arranged circularly. The inner coat consists of flattened endothelial cells united edge to edge by a cement-substance, some loose connective tissue, and a thick elastic lamina next the middle coat. The middle coat of the large

arteries, such as the aorta, contains a large proportion of elastic tissue and a correspondingly small amount of muscle, whereas that of the smallest arteries (arterioles) is purely muscular.

The *capillaries* form a dense network round and among the tissue-elements in almost every part of the body, and consist of a single layer of flattened cells united by cement-substance; plain muscle-fibres of a peculiar branched shape lie outside the endothelial coat, which is encircled by their fine processes. These contractile cells (Rouget cells) do not cover the whole capillary, but are sufficiently numerous to impart to the tube the property of sometimes contracting down to such an extent as to obliterate the lumen. The calibre of the capillaries varies slightly, but the average diameter is little wider than that of a red corpuscle.

The *veins* possess three coats, but their walls are thin, contain much less muscular and elastic tissue than the arteries, and are strengthened by the presence of a considerable amount of fibrous tissue, especially in the outer coat. Most veins have valves, consisting of fibrous tissue covered on each surface by endothelial cells, and so arranged that they allow blood to flow towards the heart, but prevent any flow in the opposite direction.

The arteries remain patent when divided, and a high internal pressure is required to distend their thick muscular and elastic walls, whereas the thin-walled veins collapse when opened and become distended under a very low internal pressure.

THE COURSE OF THE CIRCULATION.—The heart beats rhythmically and usually gives sixty to eighty beats a minute. The beat consists of the contraction of the auricles, followed almost immediately by that of the ventricles, and is succeeded by a pause, during which the whole heart is completely relaxed. The contraction of the auricles and ventricles is spoken of as auricular or ventricular *systole*, the period of relaxation being called *diastole*. At each beat the ventricles expel blood into the aorta and pulmonary artery, from which it is distributed by the former to the body as a whole and by the latter to the lungs.

The blood entering the aorta from the left ventricle is conveyed by the arteries arising from it to the capillaries of the various organs of the body, with the exception of the lungs. From these organs it is returned by veins, which unite with each other, eventually forming the *venæ cavæ*; these open into the right auricle. The blood passes from the right auricle into the right ventricle, from which it is forced into the pulmonary artery; it then flows along the subdivisions of this artery through the pulmonary capillaries into the pulmonary veins (two from each

lung), and thence into the left auricle. From the left auricle the blood enters the left ventricle and is again sent out into the aorta. (See Fig. 28.)

In the abdomen, the blood passes through a double set of capillaries. The veins from the digestive tract and spleen unite to form a single large vein, the portal vein, which on reaching the liver again breaks up into capillaries; these open into the hepatic veins, which join the inferior vena cava. This arrangement is called the *portal circulation*.

The complete circulation consists, therefore, of two parts, the one from the right side of the heart through the lungs and back to the left side of the heart, known as the *pulmonary* or *lesser* circulation, and the other from the left side of the heart throughout the rest of the body and back to the right auricle, forming the *systemic* or *greater* circulation. As the blood traverses the lungs it takes up oxygen, becoming arterial blood, scarlet in colour. Arterial blood is found in the pulmonary veins, in the left side of the heart, and in the systemic arteries. During its passage through the capillaries in the various tissues the blood loses much of its oxygen, receives carbon dioxide, and becomes venous blood, darker in colour. The venous blood is carried along the systemic veins to the right side of the heart and into the pulmonary artery to take up a further supply of oxygen from the lungs.

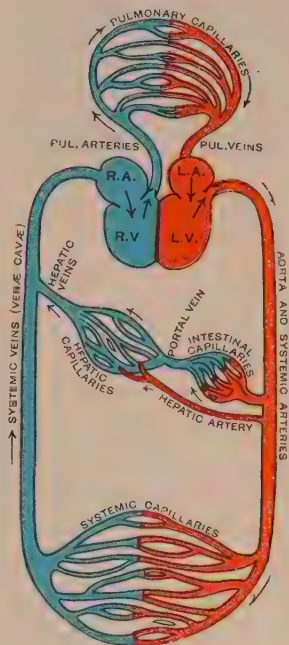


FIG. 28.—Diagram showing the course of the circulation.

Red represents arterial blood; blue represents venous blood. R.V., right ventricle. L.V., left ventricle.

SECTION II

THE PROPERTIES OF THE CARDIAC MUSCLE.—If a fine thread is tied round the apex of the frog's heart and attached to a light lever supported by a spring, a graphic record of the heart-beats can be obtained; this shows a small fall corresponding with each auricular contraction, and a larger fall corresponding with each ventricular systole (Fig. 29). A thread, tightly tied at the junction between the sinus and the auricles, will now bring the auricles and ventricle to a standstill for a variable time, since the

ligature prevents the passage of the normal rhythmic stimuli from the sinus to the rest of the heart; this is known as the Stannius ligature. The quiescent ventricle may then be used to study the properties of cardiac muscle as compared with those of skeletal muscle.



FIG. 29.—Tracing of the normal heart-beat in the frog. Downstroke = systole.

THE ALL OR NONE LAW.—The contraction of cardiac muscle shows the following characteristics: When the ventricle is stimulated with single shocks of gradually increasing strength,

it is found that with a certain strength of current the heart gives a beat. If a stronger current is used, the resulting beats are not increased in extent or force. If the heart beats at all in response to a stimulus, its contraction is maximal, whatever the strength of the stimulus. This is known as the “all or none law.” It is due to the fact that the heart-muscle is a syncytium, and that a stimulus applied at any point will, if it is effective, spread over the whole muscular tissue of the heart, and therefore every fibre will contract in response to the stimulus. The heart gives the best beat of which it is capable at any moment, though the force with which it beats varies from time to time, being influenced by various factors, including the nutritive condition of the fibres. The “all or none law” means that the heart-beat is maximal for the conditions under which the heart is placed at any moment, and not that it remains constant throughout life. In this respect cardiac muscle behaves like the individual fibres of a skeletal muscle, which also obey the “all or none law.” (See page 25.)

THE STAIRCASE EFFECT.—If the resting heart is stimulated by successive induction shocks at intervals of five to ten seconds, the extent of the second contraction is rather greater than that of the first. At the third or fourth contraction a maximum is reached, and succeeding contractions are all of the same extent. This phenomenon is called the “staircase effect,” and is due to the beneficial influence of the first two or three stimuli on the contractile power of the heart-muscle. A similar effect may be observed in skeletal muscle when a rather heavy lever is used, but in this instance is really due to an early stage of fatigue, which, by slowing down the contractile process, enables the heavy lever to be moved more efficiently by an equal or even by a weaker contraction.

THE REFRACTORY PHASE.—When the quiescent heart is made to beat by a single induction shock, and a second shock is sent into the heart during the systole evoked by the first stimulus,

the second stimulus produces no visible effect on the heart, which is said to be "refractory." This "refractory period" extends from the instant when the first stimulus is applied until the end of the systolic phase. Owing to the greater length of the refractory period of cardiac muscle as compared with that of skeletal muscle, it is impossible to tetanise the heart, since only those stimuli which fall during the diastolic period are effective.

The refractory period also accounts for the effects observed in the normally beating heart when a single shock is sent into the ventricle at the beginning of diastole. In this case the ventricle responds with a premature contraction, and the next stimulus coming down from the sinus to produce a ventricular systole falls within the refractory period of this premature beat and is ineffective. There is consequently a long pause, which is known as the "compensatory pause," between the premature contraction and the next beat originating from the sinus (Fig. 30).

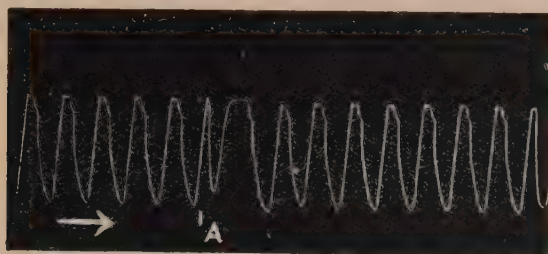


FIG. 30.—Tracing of a normally beating frog's heart. A single induction shock, applied to the ventricle at A, caused a premature systole, followed by a compensatory pause. Downstroke = systole.

CHRONAXIE.—Reference has already been made to chronaxie when dealing with muscle (see p. 31) and with nerve (see p. 51). The shorter the chronaxie, A, the shorter the refractory period, C, and the action current, E, and the summation interval, G, as shown in the following table:—

	A	C	E	G
Frog's nerve . . .	0·003	0·003	0·0008	0·0005
Sartorius . . .	0·02	0·01	0·01	0·0015
Ventricle . . .	2·00	0·2	2·3	0·008

Somewhat similar relationships have been pointed out by Lewis in the case of the heart-tissues:—

	Fibre Size.	Rate of Conduction.	Duration of Systole.	Refractory Period.
Sino-auricular node of heart . . .	1	1	(4)	4
Ventricle of heart . . .	2	2	3	3
Auricle of heart . . .	3	3	2	2
Purkinje fibres of heart . . .	4	4	(1)	1

Figures in brackets as yet theoretical.

EFFECT OF LENGTH OF FIBRES.—(4) The force of the contraction is influenced, as in the case of skeletal muscle, by the length of the cardiac fibres (p. 27). If the heart is isolated and perfused with saline solution (0·65 per cent. NaCl), the force of the ventricular contraction will vary with the pressure under which the fluid is allowed to enter the heart. The higher the pressure, the greater will be the amount of saline solution entering the ventricle during diastole, and the greater will be the length of each of its fibres at the end of diastole. The greater diastolic length of the fibres enables the heart-muscle to contract more strongly during systole, with the result that the heart empties itself as completely as it did when the pressure of the perfusing fluid was low. This important phenomenon, which will be referred to later, was called by Starling the “Law of the Heart.”

Further, increase of the internal tension to which the fibres are exposed is a stimulus to contraction, and it is for this reason that the apical half of the frog's ventricle contracts rhythmically when it is filled with fluid under pressure. The heart of the snail is so susceptible to this stimulus that it will not beat at all unless its fibres are under tension.

THE NUTRITION OF THE HEART-MUSCLE.—The nutrition of the heart-muscle is dependent on the amount and composition of the nutrient fluid supplied to it; normally this fluid is the circulating blood. The influence of alterations in the composition of the nutrient fluid is very easily studied in the isolated (or surviving) frog's heart, the muscular wall of which is nourished

entirely by interchanges between the muscular fibres and the blood flowing through the heart. For this purpose a cannula (Symes'), such as that shown in Fig. 31, is tied into an auricle, and the heart is excised. The cannula is attached to a bottle containing a suitable perfusion-fluid, which enters the heart at a pressure of 1 to 2 cm. of water. The fluid expelled through the bulbus arteriosus from the ventricle flows over

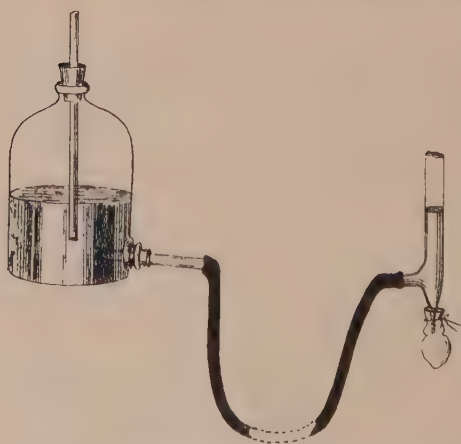


FIG. 31.—Diagram of apparatus for perfusion of frog's heart.

the surface of the heart, keeping it moist. The apex of the ventricle is connected by a thread with a recording lever.

The perfusing fluid most commonly used for the frog's heart is known as Ringer's fluid, and has the following composition : —

NaCl		0.65	per cent.
KCl		0.03	„
CaCl ₂		0.02	„
A trace of sodium bicarbonate.			

If 0.1 per cent. glucose is added to this solution, it is called Locke's fluid.

By means of this or similar methods, the influence of changes in the composition of the perfusing fluid upon the rate and force of the beat can be readily ascertained. The muscle of the frog's heart possesses a large store of energy, and will continue to beat for a long time without any fresh supply of nutrient material so long as the perfusing fluid contains oxygen. The force of the beat is dependent, however, not only on the supply of oxygen, but also on the presence or absence of certain salts, and on the reaction of the perfusing fluid.

THE IMPORTANCE OF CALCIUM.—(1) If the heart is perfused with a solution free from calcium, the contractions of the ventricle gradually become feebler, and the heart soon stops in diastole. When calcium, but not potassium, is present, the ventricle after a short time fails to relax completely during diastole, and eventually may come to a standstill in a fully contracted state. The presence of both calcium and potassium, as, for example, in Ringer's fluid, seems to be essential for the maintenance of the normal beat.

(2) The heart is extremely sensitive to slight changes in the reaction, that is, the H ion concentration, of the perfusing fluid. It beats most forcibly when the perfusing fluid is neutral; if the fluid is made slightly acid or slightly alkaline, the beats become smaller.

THE CORONARY ARTERIES.—In the mammal the heart receives its blood-supply through the coronary arteries, along which blood is flowing during both systole and diastole. The conditions which modify the supply of blood to the heart by the coronary vessels can be readily studied in the heart-lung preparation (p. 109), with the addition of a cannula being placed in the coronary sinus, so that the blood flowing through the coronary vessels can be collected and measured. In the first place, the amount of blood flowing through the coronary

vessels varies directly with the blood-pressure in the aorta. In the second place, CO_2 and other metabolic products of the activity of the heart increase the coronary blood-flow since they dilate the coronary vessels. By one or both of these means the supply of blood and, therefore, of oxygen and nutritive material to the heart is increased whenever the heart does more work. The more important factor is the arterial blood-pressure, and a rise of 50 mm. Hg in the arterial pressure may treble the supply of blood to the heart. The coronary blood-flow is also increased by the addition of adrenaline to the circulating blood, since this substance dilates the coronary vessels.

If the supply of oxygen and of nutrient material to the heart becomes inadequate for its needs, the nutrition of the muscle-fibres is impaired, and the contractile power of the heart is diminished. When the supply of blood to the heart (or a large part of it) is abruptly cut off by ligation of a coronary artery, or of one of its main branches, the ventricles almost immediately cease to contract, and the heart cannot be made to beat again.

THE ACTION OF DRUGS ON THE HEART.—The action of drugs on the heart is most easily studied in the mammalian heart perfused with warm oxygenated Locke's fluid. The rate of the heart-beat is slowed by pilocarpine or muscarine, which stimulate the vagus endings in the heart; this effect is abolished by atropine, which paralyses these endings, so that after its administration stimulation of the vagi has no effect on the rate of the heart. Atropine has no action on the accelerator nerve-endings. Nicotine first stimulates and then paralyses the cell-stations of the vagus in the heart; if it is painted on the frog's heart, stimulation of the vagus trunk is ineffective, since the impulses passing along it are blocked at the cell-stations. Adrenaline stimulates the nerve-endings of the accelerator nerves, thereby increasing both the force and the frequency of the beat of the excised heart.

THE EFFECT OF TEMPERATURE.—Both in the frog and in the mammal the rate of the heart is increased by a rise, and decreased by a fall, in the temperature of the fluid circulating through it.

SECTION III

THE CAUSATION OF THE HEART-BEAT.—It was formerly supposed that the beat originated in the nerve-cells of the heart, from which a regular series of stimuli was sent out to the heart-muscle. The view now universally held, however, is that the cardiac muscle possesses an inherent power of rhythmic

contraction, which is most marked in the sinus and least so in the ventricle, and that this rhythmic power can exist absolutely independently of the nervous system, although, as will be seen later, it can be influenced by impulses passing along the nerves to the heart. This view is known as the *myogenic* theory of the heart-beat. The myogenic theory has been accepted because it was shown that the apical half of the frog's ventricle, or a strip of the ventricle of the tortoise, if kept stretched and moist, can be made to beat rhythmically without any external stimulus, although subsequent histological examination shows that neither tissue contains any nerve-cells.

It may be concluded, therefore, (1) that the rhythmic contraction of the heart is myogenic in origin, and (2) that, although all parts of the heart possess some rhythmic power, the beat normally always starts in the sinus, in which this power is most fully developed. The sinus sets the pace of the heart, and the ventricle responds to the stimuli reaching it, doing its work under the control of the sinus.

THE SINO-AURICULAR NODE.—In the mammalian heart, the sinus, although present in early embryonic life, does not exist as a separate structure after birth, but is represented by a mass of specialised tissue, lying close to the entrance of the superior vena cava into the heart and extending a little way along the sulcus terminalis of the right auricle. This tissue is known as the *sino-auricular node*.

THE AURICULO-VENTRICULAR BUNDLE.—It has already been mentioned that connecting the auricles and ventricles is a band of tissue known as the *auriculo-ventricular bundle* (bundle of His). This bundle starts near the opening of the coronary sinus into the right auricle, its point of origin being called the *auriculo-ventricular node*. It passes along the top of the interventricular septum for a short distance, and then divides into two branches, one of which runs down the right, and the other down the left, wall of the septum immediately under the endocardium. In some animals, *e.g.* the calf, it can be readily dissected out in this part of its course as a thin band, paler than the rest of the ventricular muscle. It soon breaks up into a number of very fine branches which are distributed partly to the papillary muscles, and partly over the rest of the wall of the heart. The extent of this branching is well seen in Fig. 32. The main bundle is composed of small, somewhat fusiform fibres, which are faintly striated. It is richly supplied with blood-vessels, and contains nerve-cells and nerve-fibres. The terminal

branches of the bundle consist of fibres, called *fibres of Purkinje*, which are larger and paler than ordinary cardiac muscle-fibres.



FIG. 32.—Diagram to show the distribution of the auriculo-ventricular bundle (in red) in the wall of the left ventricle. (After Tawara.)

They show striated fibrillar material on the surface, and undifferentiated protoplasm internally. Like cardiac muscle they are built up of segments, each of which has one or two nuclei in its central protoplasm.

THE RHYTHM OF THE MAMMALIAN HEART.—Although the heart is provided with many nerve-cells, and receives in addition a nerve-supply from the central nervous system, its rhythm in the mammal, as in the frog, is of myogenic origin and depends solely upon the inherent rhythmic power of the muscle itself. It has been shown, for example, that, provided they are adequately supplied with oxygenated blood, strips of mammalian ventricle will continue to beat for some hours although they contain no nerve-cells. Evidence to the same effect is furnished by the heart of an embryo chick, which begins to beat some days before any nerves are present in it; further, in tissue cultures (p. 21) of chick or mammalian heart-muscle, not only do the fibres grow and multiply, but may be seen under the microscope to pulsate rhythmically, though devoid of nerve-tissues.

HEART-BLOCK.—The excitation normally starts in the sino-auricular node, and, travelling over the walls of the auricles, reaches the auriculo-ventricular node. From this node, the impulse passes along the auriculo-ventricular bundle to the ventricles; and any condition which impairs the continuity of the bundle leads to a disturbance of the sequence of contraction of auricles and ventricles. In man the continuity of the bundle may be partially or completely destroyed by disease, the result being known as partial or complete "heart-block." In partial heart-block in its earliest stages, there is a delay in the rate of transmission of the impulse, so that the interval between auricular and ventricular contractions is increased (increased P-R interval in the electro-cardiogram (see p. 95), and increase of a-c interval of venous pulse). In further stages of partial heart-block only one out of every two or three auricular beats is conducted along the bundle to the ventricle, the latter beating at half or a third the rate of the auricles (2:1 or 3:1 rhythm). In complete heart-block the rhythm of the auricles is unaffected, whereas the ventricles beat at a rate varying from 30 to 40 per minute; the patient usually exhibits characteristic symptoms, and a simultaneous record of the venous and radial pulse, taken with the polygraph (p. 128), shows that the rhythm of the ventricles is quite independent of that of the auricles.

When the auriculo-ventricular bundle is divided in an animal the rhythm of the auricles remains unaltered, whereas the ventricles, after a short period of inactivity which follows the section, begin to beat at a slow rate having no relation to that of the auricles. Partial heart-block is sometimes seen in asphyxial conditions, even when the bundle is intact. Partial or complete heart-block can also be induced in the frog's heart, although this does not possess an auriculo-ventricular bundle, by compressing the muscular tissue uniting the auricles and ventricle so as to lessen or abolish its conductivity. The mammalian ventricle differs, however, from that of the frog in possessing a more pronounced rhythmic power, and, when functionally isolated from the auricles, it begins to beat almost immediately with its own slower rhythm.

It is evident that, in the mammalian heart, the auriculo-ventricular bundle is essential for the propagation of the wave of contraction from the auricles to the ventricles.

THE ELECTRICAL CHANGES IN THE HEART.—The time relations of, and the course taken by, the wave of contraction, as it travels from the sino-auricular node over the heart, can easily be demonstrated, not only in the lower animals, but even in man, by studying the electrical changes which take place at the same

time. These changes may be recorded by connecting two parts of the heart—for instance, the auricles and ventricles—with some form of galvanometer. For this purpose the string galvanometer is now most generally used. (See Fig. 33.)

The resting heart is isoelectric, that is to say, the auricles and the ventricles are at the same potential, and the thread of

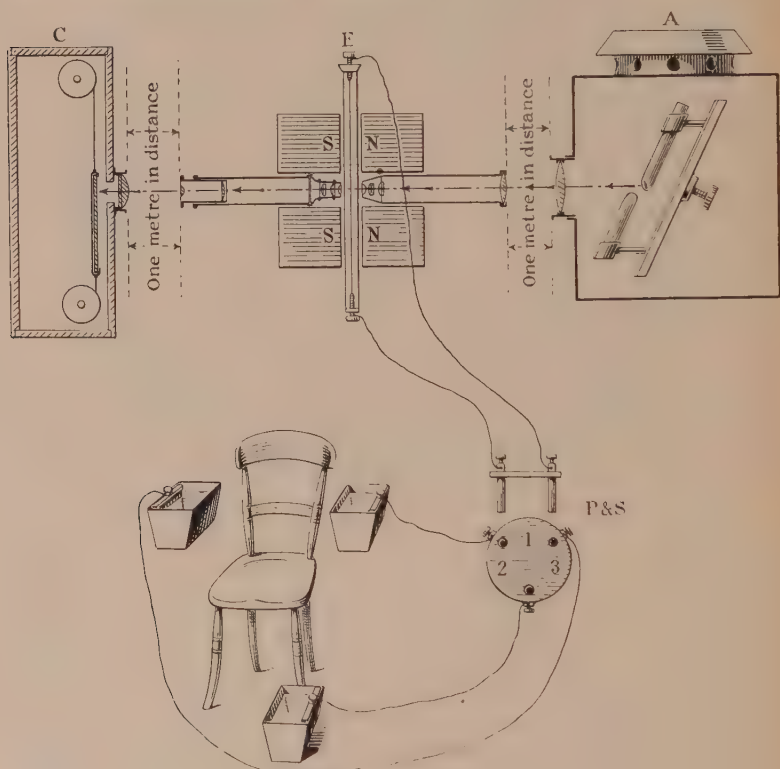


FIG. 33.—Apparatus for the electro-cardiogram.

- A = arc lamp.
- E = Einthoven quartz fibre galvanometer.
- C = camera.
- P = two-pin plug.
- S = three-hole socket.

the galvanometer is at rest. When the auricles contract, a difference of potential is set up between them and the ventricles, and a current passes in the heart from auricles to ventricles, and through the galvanometer from ventricles to auricles. During systole of the ventricles and diastole of the auricles, the current passes in the opposite direction. Contraction of the base of the ventricles while the apex is still at rest also causes a current to

flow through the string of the galvanometer. Cardiac muscle thus resembles skeletal muscle in that its contraction is accompanied by an electrical change, the contracting part being galvanometrically negative (but electro-positive) to the resting part. The difference in character of the galvanometric tracings of the electrical changes in the heart and in skeletal muscle is due partly to the prolonged contraction of cardiac muscle-fibres and partly to the complex arrangement of these fibres in the heart-wall.

THE ELECTRO-CARDIOGRAM.—Records of the electrical changes in the human heart are obtained by the apparatus shown in Fig. 33. The Einthoven galvanometer, E, consists of a silvered quartz fibre which is stretched on a holder between the poles of a powerful electro-magnet which are marked on the figure N and S. By means of the connections shown the two ends of the fibre are connected with the two pins of the plug P. The individual to be investigated when seated on the chair, places his arms in the two troughs shown in the figure which contain strong salt solution. He also places his left foot in the lower trough. Lead plates placed in these solutions connect with wires going to the three-holed socket S. By placing the plug in positions 1, 2, or 3, the quartz fibre can be connected either (1) between right and left arms; (2) between left arm and left leg; or (3) between right arm and left leg. By means of the arc lamp A, and the microscope condensers shown, a bright beam of light is focussed on the quartz fibre. This is collected again by the microscope objective and eye-piece so that a greatly magnified image of the shadow of the fibre is cast on the plate inside the camera C. When the fibre conducts a current it suffers a displacement, and a magnified image of this displacement is recorded on the plate. The apparatus is so arranged that an upward movement of the shadow of the thread on the photographic record means that the base of the heart is negative to the apex, and is therefore contracting while the apex is at rest.

Fig. 34 represents an electro-cardiogram obtained with this instrument, and shows three upstrokes for each cardiac cycle. The first wave, P, corresponds with the systole of the auricles, which, when they contract, become galvanometrically negative to the resting apex. The second wave, R, occurs at the beginning of the ventricular systole,

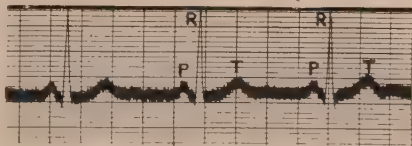


FIG. 34. —Electro-cardiogram from human heart. (Hume.) Explanation of letters in text.

The interval between the vertical lines is $\frac{1}{5}$ sec.

and is due to the systole commencing at the base of the ventricle, which becomes negative to the apex. As the wave of contraction travels to the apex, the thread returns to its resting position and remains steady for a short time, during which the whole ventricle is in contraction. The final rise at T is due to the systole lasting longer at the base than at the apex, particularly round the root of the aorta and pulmonary artery. The systole of the ventricles continues from the beginning of the R wave to the summit of the T wave. The records obtained in the lower animals show the same general form; in the frog and tortoise the prolonged contraction of the ventricle is accompanied by a long period between R and T during which the heart is isoelectric.

SECTION IV

THE INNERVATION OF THE HEART.—The nerves supplying the heart are (1) the vagus, and (2) branches from the sympathetic system. In the frog, the pre-ganglionic sympathetic fibres leave the spinal cord in the white ramus of the third spinal nerve, and have their cell-stations in the corresponding sympathetic ganglion. From this ganglion post-ganglionic fibres pass upwards to join the

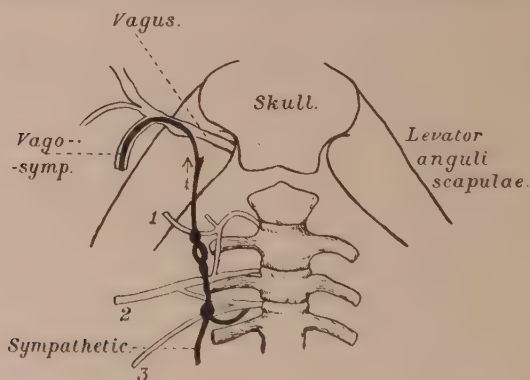


FIG. 35.—Origin of the nerves to the frog's heart.

1, 2, and 3 are spinal nerves.

vagus close to its exit from the skull; the combined vagus and sympathetic fibres form a single nerve on each side, the vago-sympathetic, which runs to the heart (Fig. 35). The fibres of the vagus nerve have their cell-stations in the ganglia of the heart itself.

In the mammal, the vagus gives off branches in the thorax, which run directly to the heart, in which their cell-stations lie. The pre-ganglionic sympathetic fibres leave the spinal cord by

the second and third thoracic white rami ; their cell-stations are in the stellate ganglion, from which post-ganglionic fibres run directly to the heart.

THE VAGUS.—When a weak stimulus is applied to the peripheral portion (*i.e.* the end towards the heart) of the divided vago-sympathetic nerve in the frog, the heart immediately beats

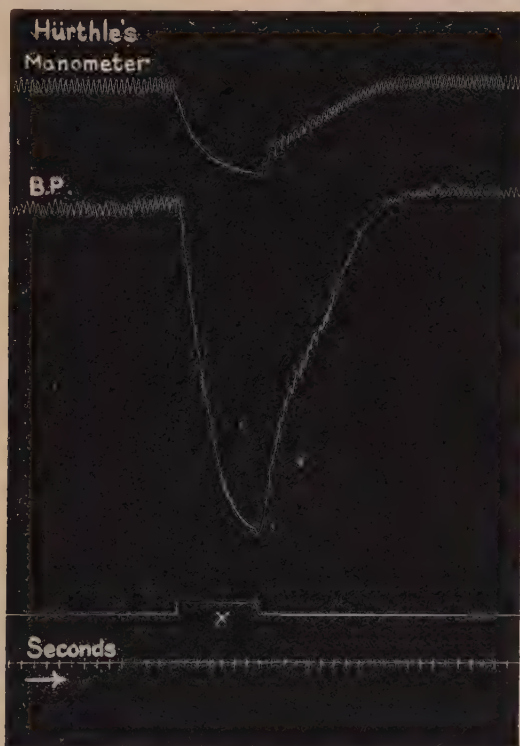


FIG. 36.—Stimulation of peripheral end of one vagus at X.

Note the inhibition of the heart and fall of blood-pressure.

B.P., arterial pressure recorded by mercurial manometer.

more slowly : a stronger stimulus brings the heart to a standstill. This effect of the vagus is known as “inhibition,” since the nerve, when stimulated, checks or inhibits the normal rhythm of the heart. When the stimulus ceases, the heart begins to beat again, at first feebly, but soon more strongly than before the stimulus was applied.

In the mammal, stimulation of the peripheral part of the vagus produces the same effect, and, if the blood-pressure is being recorded, the tracing shows a marked fall of pressure (Fig. 36). When the stimulus is removed, the heart begins to

beat again, and the blood-pressure returns to, or even rises above, its original level. Sometimes, especially if the stimulus is prolonged, the ventricle may again begin to beat slowly even during the stimulation. This phenomenon is known as "vagus escape," and is due to the fact that the ventricle is beginning to beat independently with its own normal, slow rhythm.

In the frog the vagus fibres supply not only the sinus and auricles, but also the ventricle. In many, and probably in all, mammals, the vagus fibres are distributed to the auricles, but not to the ventricles; stimulation of the vagus in this case affects only the auricles directly, and the ventricles stop beating because they no longer receive the normal stimulus from the auricles. As a rule the vagus affects chiefly the sino-auricular node, inhibiting the impulses normally originating at this point, and the whole heart is brought to a standstill. Occasionally it seems to act mainly by lessening the conductivity of the auriculo-ventricular bundle, and the auricles continue to beat at their usual rate, whereas the ventricles beat infrequently or not at all.

THE SYMPATHETIC FIBRES.—Stimulation of the sympathetic nerves to the heart, either in the frog or in the mammal, quickens the heart. For this reason the nerves are called accelerator nerves. Usually the force of the heart is also increased. The effect is only produced after a latent period of

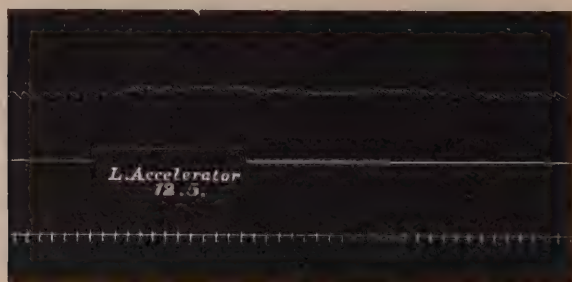


FIG. 37.—Upper tracing shows acceleration of the heart due to stimulation of an accelerator nerve.

some seconds, and lasts for a little time after the cessation of the stimulation (Fig. 37). In the mammal, with intact vagus nerves, the blood-pressure may rise slightly or may be unaffected.

CARDIAC REFLEXES.—The efferent fibres of the vagus arise from a collection of nerve-cells lying in the medulla oblongata, and known as the vagus centre. In the normal animal a continuous stream of impulses is passing from the centre down the vagus nerve, exerting a restraining force on the rate of the heart-beat and

tending to inhibit it. This action of the vagus centre is described as its *tonic* inhibitory action, and is particularly well marked in the dog and horse. Section of the vagus nerves abolishes the tonic action, and the heart beats more frequently. The tone of the vagus centre can be reflexly increased or diminished by afferent impulses reaching it from various parts of the body. The most important afferent paths are (1) the depressor nerve, (2) afferent fibres running in the vagus from the heart itself, and (3) many sensory nerves.

MAREY'S REFLEX.—The depressor nerve is purely afferent, and, starting in the walls of the aortic arch, it runs up the neck on each side, in some animals (rabbits) as a separate nerve, in others bound up with the vagus trunk, to end in the medulla

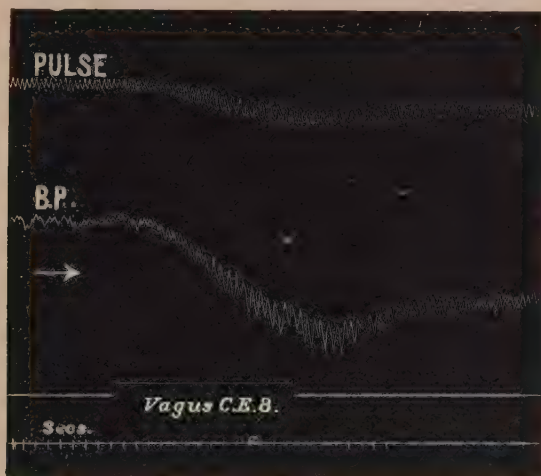


FIG. 38.—Reflex slowing of the heart due to stimulation of central end of one vagus. The other vagus is intact.

oblongata. If the nerve is divided, stimulation of its central portion (*i.e.* the end towards the brain) causes a fall of blood-pressure and slowing of the heart. The slowing of the heart is due to a reflexly produced increase of vagus tone, and does not occur when the depressor nerve is stimulated after section of the vagi. The fall of blood-pressure, however, still occurs under these conditions, which shows that the slowing of the heart is not the sole cause of the drop in blood-pressure in depressor stimulation. In animals in which the depressor nerve-fibres are bound up with the vagus nerve, stimulation of the central end of one vagus usually causes slowing of the heart, provided the other vagus is intact (Fig. 38).

When the general blood-pressure is raised, the heart is slowed, because the stretching of the aortic wall stimulates the sensory end-organs of the depressor nerve-fibres in the aorta and causes impulses to pass along these fibres to the vagus centre. This relationship between the aortic blood-pressure and the pulse-rate is known as Marey's law, which states that "the pulse-rate varies inversely with the blood-pressure."

BAINBRIDGE'S REFLEX.—It has been shown that if the flow of blood to the heart is increased, for instance, by the injection

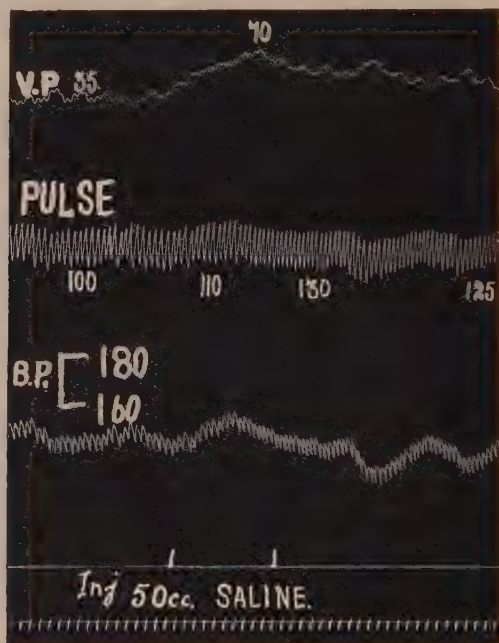


FIG. 39.—Tracing showing acceleration of the heart produced by rapidly increasing the flow of blood to the heart. The figures on the pulse-tracing represent the pulse-rate at each point. V.P., pressure in vena cava at its opening into the right auricle; the figures represent pressure in mm. water.

of fluid into a jugular vein, the venous pressure rises; at the same time the pulse-rate quickens (Fig. 39), provided the nervous supply to the heart is intact. The acceleration is due chiefly to loss of vagus tone and partly to increase of accelerator tone; it is brought about reflexly, the different impulses probably originating in the heart itself, and passing along the vagi to the medulla oblongata (Fig. 40).

This reflex operates to prevent accumulation of blood in the great veins and right side of the heart by causing acceleration of the rate of heart-beat as soon as the venous pressure begins to rise. This relation between the diastolic pressure on the right side of the heart and the pulse-rate is called, after its discoverer, Bainbridge's law. It explains why the pulse rate is accelerated during inspiration, for then there is an accelerated flow of blood to the right side of the heart. In children, and some adults, the acceleration of the pulse during inspiration is very conspicuous, the condition being called *sinus arrhythmia*. A consideration of the facts expressed by Marey's law and Bainbridge's law indicates that the rate of the pulse is controlled primarily by the heart itself. The depressor mechanism regulates the pressure on the arterial side, the accelerator reflex that on the venous side of the heart.

OTHER REFLEX EFFECTS.—The stimulation of the central end of almost any sensory nerve which, in a conscious animal, would give rise to pain, causes reflex quickening of the heart (Fig. 41),

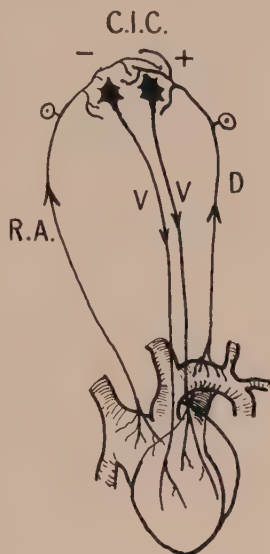


FIG. 40.—Diagram to illustrate reflex regulation of the pulse-rate.

D = depressor fibres, which increase the tone of the cardio-inhibitory centre. R.A. = afferent fibres in vagus from right side of heart which diminish the tone of the cardio-inhibitory centre. C.I.C. = cardio-inhibitory centre. V = efferent cardio-inhibitory fibres of vagus.



FIG. 41.—Reflex acceleration of the heart and rise of blood-pressure caused by stimulation of central portion of the (divided) sciatic nerve.

owing mainly to diminution of the tone of the vagus centre and partly to reflex stimulation of the accelerator nerves. Stimulation of the central end of the splanchnic nerve or of the fifth nerve, however, causes slowing of the heart, an effect which is sometimes seen to follow a severe blow on the abdomen, and which is also readily produced by irritation of the nasal mucous membrane.

Further, the rate of the heart can be modified by impulses reaching the vagus centre from the higher parts of the brain, the acceleration which takes place during emotion being partly caused in this way.

SECTION V

THE NORMAL HEART-BEAT.—Observation of the heart, exposed in an anæsthetised animal, shows that the beat begins with contraction of the great veins near the heart, and is followed immediately by the contraction of both auricles (atria), including their appendices. After a brief interval, known as the auriculo-ventricular interval, the ventricles contract synchronously, assuming the form of a short truncated cone. During their contraction the ventricles become shorter from above downwards, and, as the position of the apex remains almost unaltered, the auricles are pulled down towards the apex, and the aorta and pulmonary artery are stretched longitudinally. At the same time the cross-section of the base of the ventricles alters, becoming more nearly circular and smaller. When the contraction of the ventricles ceases, the whole heart remains for a short time at rest.

THE SEQUENCE OF EVENTS.—During diastole the blood is flowing steadily into the right auricle from the great veins, and through the auricle into the right ventricle, into which the cusps of the open tricuspid valve are hanging. When the auricle contracts, it empties most of its contents into the ventricle, and thus completes the filling of the ventricle. Since the auricular contraction begins in the muscular rings forming the termination of the great veins, there is little reflux of blood along these veins. The ventricle, which is now full of blood, contracts almost immediately after the termination of the auricular systole. The cusps of the tricuspid valve, which have already been carried towards each other by eddies set up behind them as the blood flowed from the auricle into the ventricle, are driven firmly into apposition by the pressure of the blood, their thin borders being tightly pressed together so that no blood can escape into the auricle. The contraction of the papillary muscles keeps the chordæ tendineæ taut, thereby preventing any inversion of the valve under the ventricular pressure.

The ventricle is now a closed cavity, and remains so until the pressure exerted by the contracting muscle upon the contained blood rises higher than that in the pulmonary artery. As soon as this happens, the semilunar valves open, and blood is driven into the pulmonary artery from the ventricle, which becomes nearly, but not quite, empty. When the systole of the ventricle ends, its walls relax, and the pressure in its cavity very rapidly falls below that in the pulmonary artery; as soon as this occurs, the semilunar valves close, effectually preventing any reflux of blood into the ventricle. A fraction of a second later, the pressure in the ventricle becomes less than that in the right auricle, the auriculo-ventricular valve opens, and blood, which during the ventricular systole has been flowing into the auricle from the veins, again begins to enter the ventricle. The valves open or close with the slightest difference of pressure on either side. During ventricular systole the efficiency of the tricuspid valve is assisted by the diminution of the cross-section of the base of the heart. A similar series of changes takes place simultaneously in the left side of the heart (Fig. 42).



FIG. 42.—Diagram to show the position of the mitral valve in ventricular systole (1), and in diastole (2).

A, auricle; V, ventricle.

THE CARDIAC CYCLE.—The series of events just described constitutes a *cardiac cycle*, and occupies on the average a period of 0·8 second. The cycle may be regarded as beginning with the auricular systole, which lasts 0·1 second and is followed by the ventricular systole, lasting approximately 0·3 second; during the remainder of the cycle, 0·4 second, the heart is completely relaxed. When the heart is beating slowly the duration of the cycle is lengthened, and when the heart is beating frequently it is shortened. These differences are due almost entirely to variations in the time occupied by the diastolic pause, the time taken up by the systole of the auricles and ventricles being remarkably constant.

THE "APEX-BEAT."—If the hand be placed on the chest in man, an impulse will be felt corresponding with each heart-beat. It is most distinctly felt, and is often also visible, in the fifth intercostal space, about an inch below, and slightly internal to, the nipple. The impulse is due to a combination of two causes. In the first place, the left ventricle, which lies in contact with the chest-wall and is soft and flabby during diastole, becomes hard and tense with the onset of systole. The sudden hardening of the ventricle gives a push to the soft tissues of the chest-wall with which it is in contact, thereby giving rise to the cardiac impulse. In the second place, the curved aortic arch tends to straighten out when the tension within it is raised by the entrance of blood from the heart. The same phenomenon may be readily observed in any curved elastic tube filled with fluid, into which more fluid is suddenly forced. The posterior end of the aortic arch rests against the vertebral column and ribs, and cannot alter its position; the anterior end, to which the heart is attached, is, therefore, pushed towards the chest-wall, carrying the heart with it.

Although this impulse is often spoken of as the "apex-beat," the area of the left ventricle which is in contact with the chest-wall is some distance above the actual apex of the heart. A graphic record of the cardiac impulse (cardiogram) is obtained by means of an instrument known as a *cardiograph*.

THE HEART-SOUNDS.—If one listens through a stethoscope applied to the front of the chest, two sounds are heard with each beat of the heart. They are often compared with the sounds "lūbb dūp," the first being long and low-pitched, the second short, sharp and loud.

The time relation between the heart-sounds and the other events occurring during the cardiac cycle (Fig. 43) has been determined in the following manner. A stethoscope is connected with an apparatus similar to the receiver of a telephone; the vibrations of the air in the stethoscope, set up by the heart-sounds, throw the membrane of the receiver into vibration and so alter the contact between the silver and carbon which form part of the receiver, and through which a current is passing. The current also passes through the primary circuit of an induction-coil, the secondary circuit being connected with a string galvanometer (p. 94). Each vibration of the membrane alters the strength of the current passing through the primary coil, and sets up momentary induced currents in the secondary circuit; deflections of the string of an Einthoven galvanometer are thus produced corresponding with the vibrations caused by the heart-sounds, and can be recorded on a moving photographic plate.

When a graphic record of the heart-sounds is obtained simultaneously with a cardiogram, it is found that the first sound occupies nearly the whole of ventricular systole, and that the second sound lasts for a brief space at the commencement of diastole.

The first sound is due to two causes, namely, (1) the vibrations set up by the closure of the tricuspid and mitral valves, and (2) the contraction of the muscular wall of the ventricles. When the tricuspid or mitral valves become diseased so that they fail to close, the first sound is largely replaced by a "blowing" noise, known as a murmur or *bruit*. That the contraction of the heart-muscle contributes to the first sound is shown by the fact that,

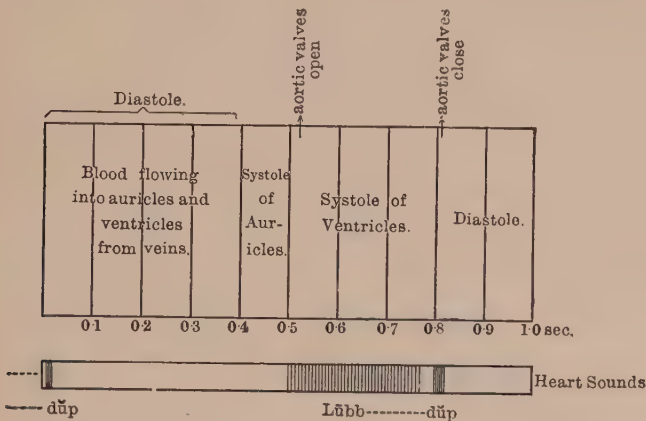


FIG. 43.—Diagram of events constituting a cardiac cycle.
(From Starling's *Principles of Physiology*.)

during the contraction of the bloodless, excised heart, a faint sound can be heard with the stethoscope, although in the empty heart the valves do not close during systole. The loudness of the first sound is chiefly determined by the magnitude of the change of endocardiac pressure at the commencement of systole, *i.e.* by the suddenness of the closure of the auriculo-ventricular valves and by the tension to which they are subjected.

The second sound is due entirely to vibrations set up in the semilunar valves by their sudden closure at the end of systole, and is replaced by a murmur if these valves are diseased, or if, in an animal, they are hooked back and prevented from closing. When the arterial blood-pressure is high, the second sound is more pronounced.

The first sound is most distinctly heard near the apex-beat; the closure of the aortic valves is best heard in the second right

intercostal space close to the sternum, and the closure of the pulmonary semilunar valves in the second left intercostal space.

SECTION VI

ENDOCARDIAC PRESSURE.—The pressure within the auricles and ventricles rises during systole and falls in diastole, and the variations in pressure are closely bound up with the other events taking place during the cardiac cycle. The changes in pressure occur so rapidly that a slowly moving fluid, such as mercury, fails to record them accurately, although a maximum and minimum mercury manometer may be employed to ascertain approximately the highest and lowest pressures occurring during a cardiac cycle. Such a manometer consists of the usual bent tube containing mercury, having interposed between it and the heart two tubes which can be used alternatively. In one tube is a valve opening towards the manometer, and in the other a valve opening towards the heart. When the blood-stream passes along the former tube, the maximum pressure is registered; when it flows along the latter, the minimum is recorded.

The pressure changes in the cavities of the heart may be studied by Hürthle's method, the essential features of which are

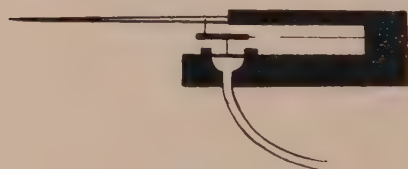


FIG. 44.—Hürthle's manometer.
(Diagrammatic.)

(1) the use of a very small manometer with a thick rubber membrane (Fig. 44), which is connected with (2) a tube opening directly into the ventricle, and (3) the filling of the whole apparatus, including the manometer, with fluid (half-saturated sodium sulphate solution).

WIGGERS' MANOMETER.—A still better manometer has been devised by Wiggers (Fig. 45). It consists of a glass tube *d*, to which is attached a brass cylinder *e*, which ends at the segmented capsule *b*, which is covered by a heavy rubber membrane tightly stretched across it. Upon this a tiny mirror *c* is fastened so that it pivots on the chord side of the segmented capsule. The lower end of the glass tube is connected by a conical joint *h* to the required cannula end *k*.

As the endocardiac pressure varies, the membrane bulges or shrinks slightly and the position of the mirror alters; these movements are recorded, and greatly magnified, by throwing on to the mirror a beam of light, which is reflected on to a

kymograph covered with photographic paper and excluded from other sources of light.

The advantages of this method are two-fold. In the first place the movements of the membrane are directly proportional to the variations in pressure, and, by the elimination of a lever, are recorded without inertia. In the second place, when vibrations are set up in the membrane, these are so frequent (250 per second) that they cannot possibly be mistaken for oscillations produced by changes in the endocardiac pressure, and are so rapidly damped that they practically do not occur when the endocardiac pressure is being recorded. A similar cannula may be passed into an artery so as to record changes in arterial pressure.

Fig. 46 represents a record, obtained by this method, of the changes of pressure in the left auricle and ventricle, and in the aorta, during a cardiac cycle. The middle curve, representing intra-ventricular pressure, shows at I a slight elevation (not always present) due to the auricular systole. This is followed almost immediately by the systole of the ventricle, which begins at II and occupies the period between II and V; it usually lasts from 0.25 to 0.3 second. At first the curve rises very steeply; the auriculo-ventricular valves close at the point II, and from II to III the ventricle is a closed cavity. At III the intra-ventricular pressure becomes higher than that in the aorta, the semi-lunar valves open, and blood flows from the ventricle into the aorta during the whole period from III to V, when the ventricle ceases to contract.

The portion of the tracing from III to V lasts about 0.18 second, and is generally known as the systolic plateau; it resembles a plateau, however, only when the arterial pressure is low, and its usual shape would be more accurately described as the systolic arch.

When the systole ends at V, the intra-ventricular pressure rapidly falls; a short distance down the descending part of the

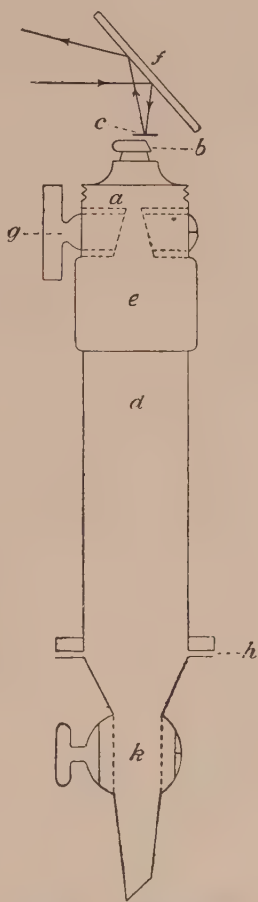


FIG. 45.—Wiggers' manometer. (From Wiggers' *The Pressure Pulses in the Cardiovascular System.*)

tracing, namely, at the point S, the pressure in the ventricle falls below that in the aorta, and the semilunar valves close. Their closure does not alter the form of the intra-ventricular record,

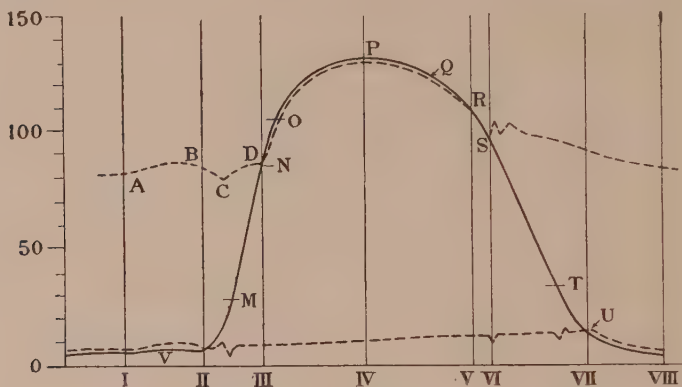


FIG. 46.—Lower dotted line the auricular pressure. The continuous line the ventricular pressure. Upper dotted line the aortic pressure. (From Wiggers' *The Pressure Pulses in the Cardiovascular System*.)

though it causes a series of small oscillations in the aortic pressure. At the point U the pressure in the ventricle falls below that in the auricle, the mitral valve opens, and blood flows into the relaxed ventricle.

AURICULAR PRESSURE.—A record of the changes of pressure in the auricle presents three main waves (Fig. 46). The first corresponds with the auricular systole, the second with the sudden closure of the auriculo-ventricular valves, and the third, which shows a steady rise during ventricular systole, is due to the filling of the auricle with blood while the auriculo-ventricular valves are still shut.

The maximum pressure in the left ventricle of the dog, as recorded by a mercury manometer, is usually from 140 to 160 mm. Hg, and in the right ventricle from 25 to 30 mm. Hg.

SECTION VII

THE OUTPUT OF THE HEART.—When the ventricles contract, they force blood into the aorta and pulmonary artery against the blood-pressure in these vessels. In so doing the heart performs work, the amount of which may be determined by the formula $W = Q \times R$, where W is the work done, Q is the amount of blood expelled from the ventricles (output of the heart)

at each beat, and R is the resistance against which the heart is working; R is approximately represented by the mean arterial pressure.

The output of the heart may be measured indirectly by enclosing the heart in an apparatus (*cardiometer*) which fits closely round the base of the ventricles, and is connected with some form of tambour and recording lever. When the ventricles contract and expel blood into the arteries their volume diminishes, and, since the apparatus is air-tight, there is a corresponding fall of the recording lever.

One of the simplest forms of cardiometer is a glass vessel, resembling a large thistle funnel, the mouth of which is covered by a rubber membrane, with a hole in its centre. When the heart is placed in the cardiometer, the border of the membrane fits closely in the auriculo-ventricular groove, forming an air-tight junction. The cardiometer is attached to a piston recorder, which is more sensitive than an ordinary tambour and consists of

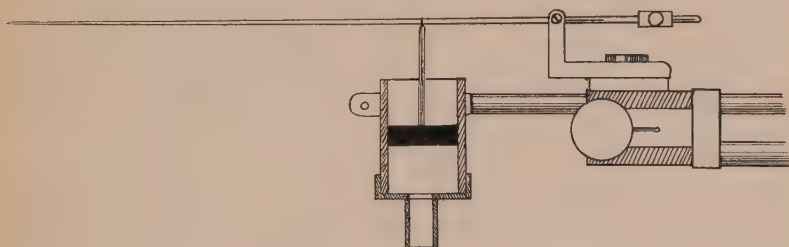


FIG. 47.—Piston recorder. (Diagrammatic.)

a vulcanite piston fitting closely in a cylinder, the latter having an opening at its lower end by which it can be connected with the cardiometer: a light counter-weighted lever is attached to the piston (Fig. 47). The piston moves very easily, and its excursions are proportional to the changes in volume of the heart. In order to obtain a quantitative measurement of the output of the heart the instrument is calibrated.

HEART-LUNG PREPARATION.—Another and direct method of determining the output of the heart in an animal is the heart-lung preparation (Fig. 48) devised by Knowlton and Starling. The common carotid artery, the descending aorta and the inferior vena cava are ligatured, and cannulae containing normal saline solution to which hirudin has been added are placed in the innominate artery and the superior vena cava. The blood leaving the left ventricle through the innominate artery passes through a thin

rubber tube A; this is enclosed in a glass tube, and can be compressed to any desired extent by means of a pump C and pressure-bottle D, the resistance thus offered to the flow of blood through the tube replacing the resistance of the arterioles. The cannula in the artery is also attached to a mercurial manometer F, which records the arterial pressure. The small cylinder E contains air, forming an air-cushion, and to some extent replacing the elasticity of the arterial wall. After traversing the tube A, the blood enters

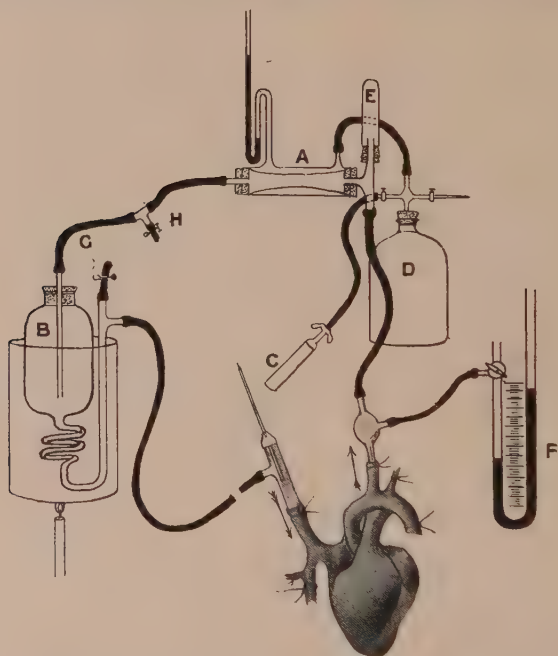


FIG. 48.—Arrangement of apparatus in the heart-lung preparation.
(Knowlton and Starling.) Description in the text.

a cylinder B in which it is warmed, and from which it passes into the superior vena cava, and then through the lungs to the left side of the heart. The circulation is thus confined to the heart and lungs, artificial respiration being maintained by a pump. The output of the left ventricle in a given time, *e.g.* five seconds, can be measured by clamping the tube G, opening the clip on H, and allowing the blood to flow into a graduated vessel instead of into the cylinder; and if the rate of the heart is observed, its output at each beat can be calculated.

THE HEART OUTPUT PER MINUTE.—This is sometimes called the minute volume. One method of measuring it is to

ascertain (a) the O_2 percentage of arterial blood; (b) the O_2 percentage of mixed venous blood; and (c) the O_2 used per minute. Then every 100 c.c. of blood passing through the lungs gains the difference between (a) and (b). Call this (a-b). Then (c) divided by (a-b) and multiplied by 100 = volume of blood passing through the lungs per minute, that is, heart output per minute. Example for a man engaged in active exercise: (a) = 19 per cent., (b) = 7 per cent., and (c) = 3000 c.c. Then

$$\text{output} = \frac{100 \times 3000}{19 - 7} = 25,000 \text{ c.c., i.e. 25 litres per minute.}$$

If pulse-rate was 125 beats per minute, the output per beat was 200 c.c.

NITROUS OXIDE METHOD.—In man, the output of the heart has been indirectly determined in the following manner. The individual takes a deep breath of air containing a certain amount of nitrous oxide, which is very soluble in blood. After a few seconds he expires sufficiently deeply to enable a sample of alveolar air to be collected in the manner described on p. 173. He then holds his breath for twenty to thirty seconds, and again expires deeply, a second sample of alveolar air being collected. The interval between the two expirations is called the experimental period; and during this period nitrous oxide is taken up in solution by the blood as it passes through the lungs, its solubility being such that 1 c.c. of blood, if exposed to an atmosphere of pure nitrous oxide, will take up 0.43 c.c. of the gas. The total amount of air in the lungs at the beginning and end of the experimental period between the two expirations is determined by indirect means.

From these data the amount of blood passing through the lungs in a minute can be calculated. To take an example, the volume of air in the lungs at the beginning of the experimental period is 3.25 litres, and it contains, as shown by the analysis of the first sample, 12 per cent. of nitrous oxide; the total quantity of nitrous oxide in the air of the lungs is $\frac{3250 \text{ c.c.} \times 12}{100} = 390 \text{ c.c.}$

At the end of the period the total volume of air in the lungs is 3 litres, and the percentage of nitrous oxide in the second sample of expired air is found to be 10 per cent. Consequently the lungs contain 300 c.c. of nitrous oxide. Thus 90 c.c. of nitrous oxide have been taken up by the blood; and the average percentage of nitrous oxide in the air in the lungs is $\frac{12 \text{ per cent.} + 10 \text{ per cent.}}{2} = 11 \text{ per cent.}$

With this percentage of nitrous oxide in the air of the lungs,

each 1 c.c. of blood passing through them will take up $\frac{0.43 \times 11}{100} = 0.047$ c.c. of nitrous oxide; and in order to take up

90 c.c., 1.9 litres of blood must have passed through the lungs during the experimental period. If the experimental period lasted twenty-seven seconds, the flow of blood through the lungs per minute is 4.2 litres. This figure represents the output from the right ventricle during that period, and, if the pulse-rate is 70 per minute, the output per beat will be $\frac{4200 \text{ c.c.}}{70} = 60$ c.c. per beat.

This figure may be taken as representing the average output of each ventricle in man at rest, since the output of the two ventricles is the same.

THE WORK OF THE HEART.—The mean arterial pressure in man is about 90 to 100 mm. Hg. From these data the work done by the heart at each beat can be calculated. Thus $Q \times R = 60 \text{ gm.} \times 0.100 \text{ metre} \times 13.6$ (specific gravity of mercury being 13.6 times that of blood) = 81.6 gramme-metres. This figure represents the work done by the left ventricle. If the pressure in the pulmonary artery be taken as 20 mm. Hg, the work done by the right ventricle will be $60 \text{ gm.} \times 0.02 \text{ metre} \times 13.6 =$ approximately 16.4 gramme-metres. The total work of the heart, therefore, is in this instance 98 gramme-metres per beat.

The heart expels blood not only against the peripheral resistance, but with a certain velocity. The work (W) done in imparting this velocity to the blood is measured by the formula $W = \frac{QV^2}{2g}$, where Q = mass of blood expelled, V = its velocity during the systolic period, g = the force of gravity; it amounts when the output is small to only 1 to 2 per cent. of the total work of the heart, but the amount rapidly increases with increased output of the heart, and with large outputs may amount to 10 per cent., or more, of the total work.

SECTION VIII

EFFECT OF STARLING'S LAW.—It has already been pointed out (p. 27) that, when a skeletal muscle contracts, the contractile stress developed in it is proportional to the initial length of its muscle-fibres, *i.e.* its length just before it begins to contract, and that if the muscle is stretched by means of a weight, or if, in an

isometric contraction, its fixed length be increased, it contracts more forcibly. The heart-muscle behaves in exactly the same way; but, since the heart is a hollow organ, the initial length of its fibres, that is, their length at the end of diastole, depends upon

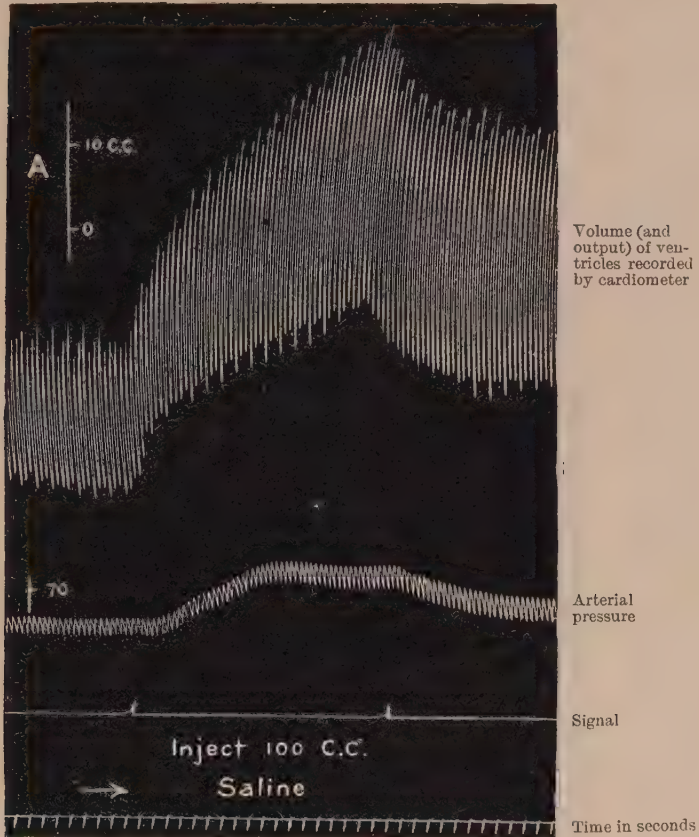


FIG. 49.—Tracing to show the effect of increased diastolic filling of the ventricles upon their output and volume. The venous inflow was increased by injecting saline solution into a vein. The heart was enclosed in a cardiometer: downstroke = systole. A = calibration of cardiometer.

the amount of blood present in its cavities. If the heart is distended with blood each fibre will be longer than if it contains but little blood, and the greater the initial length of its fibres, the greater will be the force with which it contracts during systole. The fact that the contractile power of the heart-muscle varies with

the length of its fibres at the end of diastole, or, in other words, with the volume of the heart at the end of diastole, has been termed by Starling *the law of the heart*. It follows, therefore, that the amount of blood expelled from the ventricles at each beat is determined by the degree to which they are filled at the beginning of systole; and, if the arterial pressure is steady, this depends on the amount of blood entering the heart during diastole. This amount is increased (1) by deeper respiratory movements, whereby more blood is sent into the heart with each inspiration; (2) by muscular movement, which drives blood along the veins towards the heart; and (3) by any increase in the total volume of the circulating blood, such as is produced by the injection of blood or saline solution into a vein (Fig. 49). During muscular exercise, the more forcible respiration and the active muscular

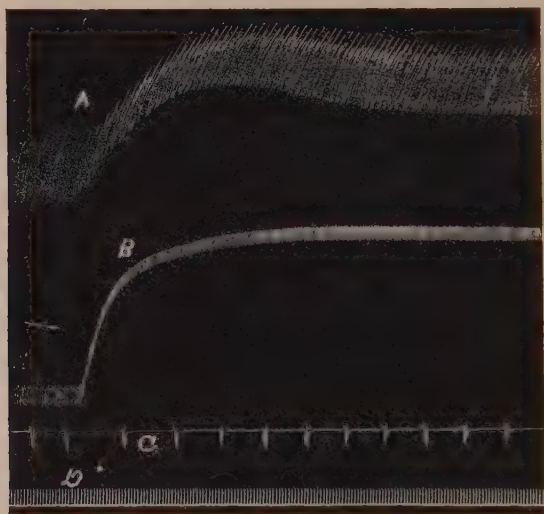


FIG. 50.—Effect of a rise of arterial pressure upon the output of the heart. (Knowlton and Starling.)

A, volume of ventricle; B, arterial pressure; C, output of left ventricle; D, time in seconds.

movement lead to a much larger flow of blood into the heart and, therefore, to a larger output of blood than during rest.

The output of the heart is not affected, except for a few moments, by alterations in the arterial blood-pressure, unless these are extreme. The first effect of a rise of blood-pressure is that for a few beats the output of the ventricles becomes smaller; and, since the amount of blood entering the heart during each diastole is unchanged, the volume of the heart gradually becomes

larger. The greater distension of the ventricle increases the length of its fibres, causing them to contract more and more forcibly during systole and thus to expel more blood into the aorta. The result is that the heart soon becomes so dilated at the end of diastole, and therefore contracts so strongly during systole, that its output per beat becomes as large as it was at the lower arterial pressure (Fig. 50). In the normal animal, the presence of the pericardium prevents the risk of over-distension of the heart.

THE POWER OF COMPENSATION.—The capacity of the ventricle to maintain its normal output in spite of a greatly raised arterial pressure, and to increase its output when the venous inflow becomes larger, is spoken of as its “reserve” force or “power of compensation,” and is of the utmost importance. In its relation to the body as a whole the output of the heart is one of the fundamental facts of the circulation, since it determines the rate at which oxygen can be carried from the lungs to the tissues ; and if the output were diminished whenever the blood-pressure rose, for example during exercise, the high blood-pressure would necessarily involve a smaller, and possibly inadequate, supply of oxygen to the tissues.

The compensatory power of the heart enables it to adapt itself to transient variations in arterial blood-pressure and venous inflow. When the work of the heart is permanently increased, for example, by a continuously high blood-pressure, the heart-muscle hypertrophies, just as skeletal muscles enlarge as the result of regular muscular work.

When the heart beats rapidly, the diastolic pause is shortened, less blood enters it between the beats, and its output per beat is diminished. Consequently its output in a given time (*e.g.* a minute) is not necessarily greater when the heart is beating rapidly than when it is beating slowly. If the inflow of venous blood to the heart is small, the blood enters the ventricles at a fairly uniform rate during diastole ; and an increase in the rate of the heart merely causes a correspondingly smaller output per beat, the output per minute being almost unaltered (Fig. 51, A). If, however, the flow of blood into the heart during diastole is large, the ventricles become almost fully distended with blood early in diastole, and very little additional blood passes into them later in diastole. In these circumstances, an increase of rate, that is to say, a shorter diastole, leads to very little diminution of the output per beat and to a considerable increase in the output per minute (Fig. 51, B). Hence, when the venous inflow is large, acceleration of the heart increases its maximum output by

enabling it to discharge more blood into the arteries in a given time than would be possible at the slower rate.

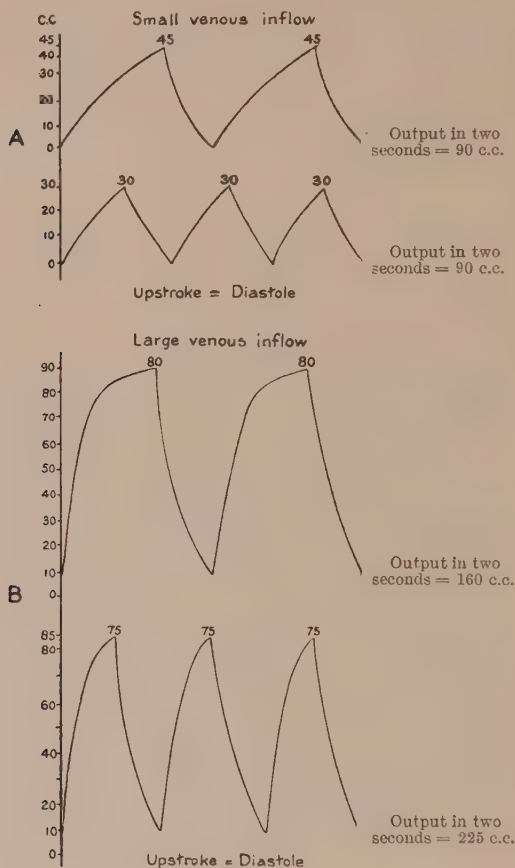


FIG. 51.—Diagram to illustrate the influence of the rate of the heart upon its output, (A) when the venous inflow is small, (B) when the venous inflow is large. The ventricle is assumed to empty itself completely during systole when the inflow is small, but not quite completely when the venous inflow is large.

The factors which control the output of the heart may be summarised thus :—

- (1) If the rate of the heart is constant, the output of the ventricles varies directly with the venous inflow to the heart during diastole, but is (within wide limits) unaffected by changes of arterial pressure.

- (2) If the venous inflow is small, the output per minute is independent of the rate of the heart; if the venous inflow is large, acceleration of the heart increases its output.

VARIATIONS IN THE WORK OF THE HEART.—Since the work done by the heart is roughly measured by its output, multiplied by the arterial pressure ($Q \times R$), it will be altered either by a rise or fall of arterial pressure or by variations in the output of the heart, or by these two factors varying simultaneously. Whenever the arterial blood-pressure rises, the heart does more work, since the output remains unchanged. Again, increased filling of the heart during diastole, brought about by any of the causes already mentioned, by increasing its output, will add to the work of the heart; and the larger output from the heart tends in itself to raise the arterial blood-pressure, and thus to increase still further the work done. In muscular exercise there is both a rise in arterial blood-pressure and a greater diastolic filling of the heart.

In man, during muscular exercise, the output of the heart per beat may be 90 to 100 c.c. or even more, and, since the heart is beating much more frequently than during rest, its output per minute may be three or four times as great as during rest, its work being thereby largely increased. These facts indicate how important it is that persons whose hearts have become less efficient owing to disease should refrain from excessive exercise.

CHAPTER VI

THE VASCULAR SYSTEM

SECTION I

THE BLOOD-PRESSURE.—When an artery is cut across, the blood spurts out from its central end (the end nearest the heart) with considerable force and for some distance ; and, evidently, the blood contained in the arteries is exerting a high pressure upon the wall of the vessels. When a vein is divided, the blood escapes from its peripheral end in a slow, steady stream.

If a vertical glass tube be tied into the central end of a divided artery, the blood will be seen to attain a height of three or four feet or more, and to show oscillations corresponding with each heart-beat. The pressure inside the artery is then equal to that exerted by the column of blood. The method is unsatisfactory, because the clotting of the blood in the tube soon brings the experiment to an end, and because, in a small animal, the loss of blood from the body may interfere with the circulatory mechanism.

THE MERCURY MANOMETER.—In measuring arterial pressure the usual procedure is to tie a cannula into the central end of the cut artery and to connect the cannula with one limb of a U-shaped manometer containing mercury. The height in millimetres of a column of mercury which just counterbalances the pressure of the blood in the arteries, and prevents the blood from escaping into the cannula, is taken as a measure of that pressure ; and the arterial pressure is said to be so many (*e.g.* 100) mm. Hg. A writing point attached to a float resting on the mercury in the other limb of the manometer can be used to record the pressure on a moving smoked surface (kymograph). The method used is shown in Fig. 52. An artery, such as the carotid or femoral, is exposed in an anæsthetised animal, and the flow of blood is shut off by a clip. The artery is ligatured about 2 or 3 cm. beyond the clip, and is opened between the clip and the ligature. A cannula containing a half-saturated solution of sodium sulphate is tied into

it. This cannula is connected by thick rubber tubing with a bottle containing a half-saturated solution of sodium sulphate, and with one limb of the manometer. By raising the bottle, the cannula and connecting tubing can be filled with sodium sulphate solution

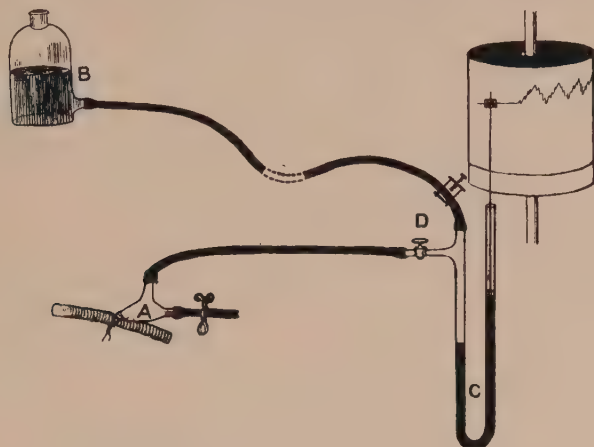


FIG. 52.—Apparatus for taking a blood-pressure tracing.

A, cannula inserted in an artery; B, pressure-bottle; C, mercurial manometer.

under such pressure that the column of mercury in the limb to which the float is attached rises from 100 to 150 mm. higher than the column in the limb connected with the artery. The connection between the pressure-bottle and the manometer is then shut off by a screw-clamp, and the clip is removed from the artery.

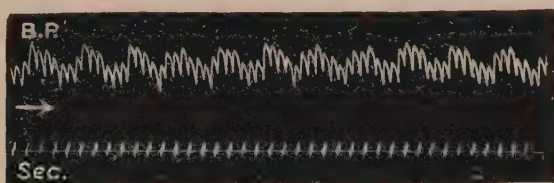


FIG. 53.—Tracing of arterial pressure.

The column of mercury rises or falls slightly until its pressure counterbalances that of the blood, and the writing lever then remains at a constant level, except for slight oscillations with each heart-beat and with the respiratory movements (Fig. 53). The height of the column of mercury, when its summit is midway between the top and the bottom of these oscillations, is measured, and is called the *mean* arterial pressure.

VENOUS PRESSURE.—The pressure in the large veins may be determined in a similar manner, except that, as the pressure is low, the whole manometer is usually filled with sodium sulphate solution.

Observations made in this way show that, whereas in a systemic artery the pressure suddenly increases with each heart-beat and falls between the beats, while the mean blood-pressure lies between 90 and 100 mm. Hg, the venous pressure amounts only to a very few mm. Hg, and is not affected by the heart-beat.

The fluctuation of arterial pressure with each heart-beat is much greater than a tracing (such as Fig. 53), made with a mercurial manometer, would lead one to suppose. This is on account of the inertia of the mercury, which prevents it from accurately following such rapid changes of pressure. By the use of the rapidly responding manometers, *e.g.* Wiggers, it is found that the pressure-fluctuation at each heart-beat is of the order of 400 mm. Hg in large arteries.

PRESSURES IN DIFFERENT VESSELS.—It is found that the arterial pressure is highest in the aorta, rather less in the medium-sized arteries, and that there is an abrupt fall of pressure in the arterioles, particularly if these are constricted by the vaso-motor

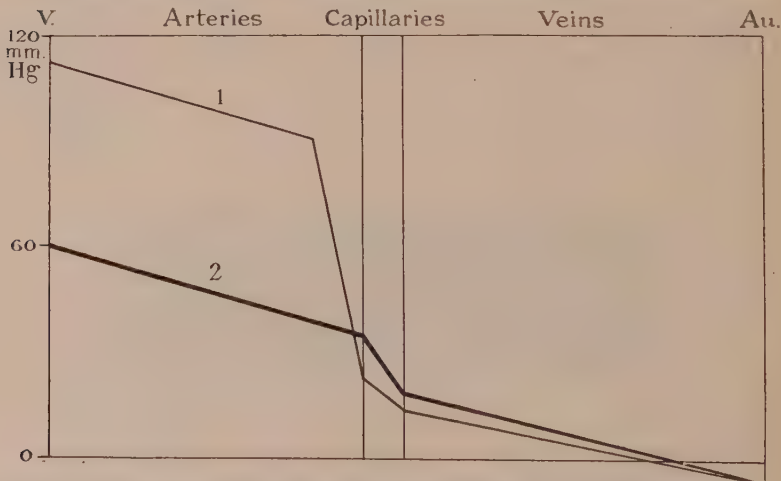


FIG. 54.—The curves show the blood-pressures at different parts of the circulatory system. (1) With arterioles constricted; (2) with arterioles relaxed.

centre. In the capillaries the pressure drops still more, and finally there is a further fall of pressure in the veins until, in the large veins near the heart, it may actually be negative, that is, less than the atmospheric pressure. These differences of pressure

are diagrammatically represented in Fig. 54. The pressure in the pulmonary artery varies from 20 to 25 mm. Hg, and on the average is about one-sixth of that in the aorta or its main branches.

FORMATION OF THE CONTINUOUS FLOW.—We may now consider the factors which are concerned in this distribution of pressure, and in the conversion of the jerky flow of blood in the arteries into a continuous flow in the capillaries and veins.

They are: (1) the beat of the heart, (2) the elasticity of the arteries, and (3) the peripheral resistance.

The action of these factors is a purely mechanical one, and can be reproduced in an artificial scheme such as is shown in Fig. 55.

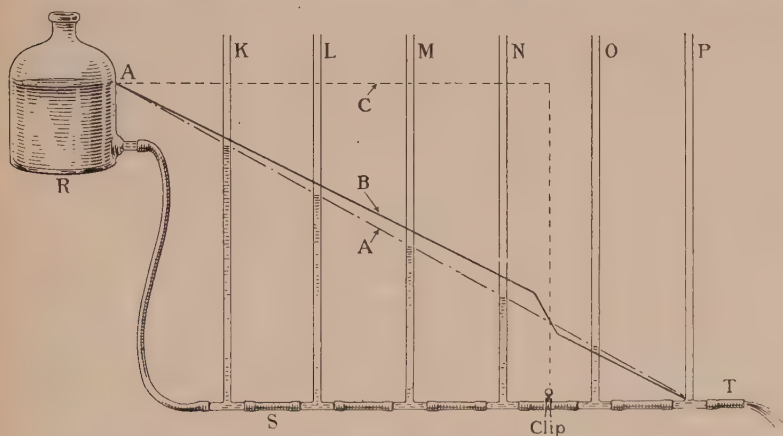


FIG. 55.—Apparatus for demonstrating the pressures at different parts of a tube down which a fluid is flowing. The dotted line shows the pressure when the clip is clamped. The full line shows the pressure when the clip is partly clamped. The broken line shows the pressure with the clamp loose.

Reservoir R containing a coloured fluid is attached to a horizontal rubber tube S T open at its other end, and a number of vertical glass tubes open at the top are connected with this tube at equal distances from one another. As the fluid flows from the reservoir, it rises in the vertical tubes to a height corresponding with the pressure at that point, and the line A, A, joining the top of the columns of fluid in the tubes, shows that there is a uniform fall of pressure along the rubber tube. The pressure falls because of the friction between the fluid and the wall of the tube; owing to the friction, there is some resistance to the flow of fluid along the tube and the hydrostatic pressure is gradually used up in overcoming this resistance. If a screw-clip is placed on the rubber tube and gradually tightened, thereby introducing a greater resistance to the flow of fluid along the tube, the pressure rises

on the proximal side, and falls on the distal side, of the clip, the pressure gradient along the tube being indicated by the full line, A, B.

When the flow of fluid from the reservoir is made intermittent by alternately compressing and releasing at short intervals the connection between it and the tube, the fluid in the vertical tubes K, L, M, and N, between the reservoir and the resistance shows corresponding oscillations in height, whereas in the tubes O and P, beyond, these oscillations are decreased, and fluid flows from the end of the rubber tube in a nearly steady stream.

In the body the reservoir is represented by the heart, which at each beat sends into the aorta a certain quantity of blood (in man about 60 c.c.). The peripheral resistance is due to friction between the flowing blood and the walls of the vessels, the amount of friction varying inversely with the bore of the vessels and with the velocity of the blood-stream. The peripheral resistance caused by this friction is very large in the arterioles, when they are contracted under the influence of the vaso-motor centre. In the capillaries the blood flows so slowly that, although their calibre is very minute, the resistance is much less than in the arterioles; and in the large venules and veins the resistance is comparatively slight.

THE EFFECT OF PERIPHERAL RESISTANCE.—With each beat of the heart an additional quantity of blood enters the arterial system, and, if there were no peripheral resistance, an equal quantity would shortly afterwards escape through the arterioles into the capillaries. But the resistance offered by the arterioles is so great that, when the blood is forced during systole into the already distended arterial system, there is not an immediate escape of a corresponding amount from the arteries into the capillaries. The force exerted by the heart at each beat is used, partly in driving the blood through the arteries into the capillaries during the beat, and partly, indeed chiefly, in distending the arteries so that they can accommodate the additional blood sent into them, while the pressure within them rises. The energy expended by the heart during systole is thus, to a large extent, stored for the time being in the arteries as potential energy; and during diastole this energy again becomes kinetic, the arteries shrinking by virtue of their elasticity and thereby forcing blood in a steady stream through the arterioles into the capillaries, with a consequent fall in the arterial pressure. The result is that an intermittent supply of blood to the aorta is converted into a continuous flow in the capillaries and veins.

When the amount of blood entering the arterial system during

systole is equal to that leaving it, partly during systole and partly during diastole, the mean arterial pressure remains steady. Any increase or decrease in the amount of blood entering the aorta at each beat will tend to raise or lower the arterial pressure. Similarly, dilatation of the arterioles will allow more blood to leave the arteries with each beat, the arteries will therefore be less distended with blood, and the pressure on their walls (arterial pressure) will diminish. Conversely, constriction of the arterioles will diminish the outflow from the arteries, and will lead to a rise of arterial pressure.

Although the driving force of the heart-pump is sufficient to propel the blood round the body and back to the heart, its action is normally assisted (1) by the respiratory movements, which will be considered later (p. 169), and (2) by skeletal muscular movements. Every muscular movement tends to squeeze blood along the veins towards the heart, any reflux being prevented by the valves with which these veins are provided.

SECTION II

BLOOD-PRESSURE IN MAN.—The highest blood-pressure occurring during the cardiac systole is called the *systolic* pressure; the pressure at the end of diastole is the *diastolic* pressure, the difference between the two being called the *pulse*-pressure. The systolic pressure is measured by means of a Riva-Rocci sphygmomanometer. This consists (Fig. 56) of a leather band about four inches wide, inside which is a rubber bag communicating with a mercurial manometer and connected with a small pressure-bulb. Attached to the bulb is a screw by which the bag can be put into communication with or shut off from, the external air.

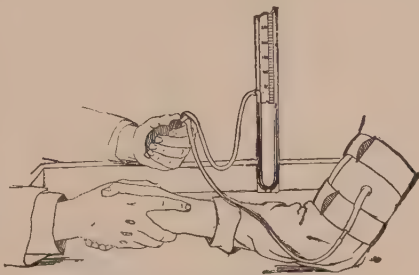


FIG. 56.—Riva-Rocci sphygmomanometer.
(From Messrs. Hawksley.)

The band and the bag are fastened round the upper arm. The observer feels the radial pulse with the fingers of one hand, while with the other he squeezes the bulb and distends the bag with air. The leather band does not stretch, and the pressure of the rubber bag, as it distends, is exerted entirely on the arm and compresses the blood-vessels; at the same time the pressure rises in the manometer. The bulb is squeezed until the pressure in

the bag is just sufficient to obliterate the brachial artery and the radial pulse disappears. When this occurs, the pressure in the bag is equal to that in the manometer, and is noted. The screw attached to the bulb is then gently turned, the air slowly escapes, and the pressure falls; when the radial pulse is just perceptible, the pressure in the manometer is again observed. The mean between the two readings is the *systolic arterial pressure*. This represents the pressure on the outer wall of the artery at which its lumen is just obliterated.

If air is allowed gradually to escape from the bag after the systolic pressure has been determined, it will be observed that at a certain point the oscillations of the mercury and the radial pulse show a maximal excursion with each beat of the heart. This is due to the fact that the systolic pressure is sufficient to distend the vessel, whereas between the beats of the heart the artery is collapsed. The pressure in the bag at this point represents the *mean* pressure, and the lowest level of the manometer *between* the beats gives a record of the *diastolic* pressure. By measuring the diastolic and systolic pressures, the *pulse-pressure*, which is the difference between them, can be determined. The systolic pressure in the young healthy adult varies in the large arteries, such as the brachial, from 100 to 120 mm. Hg; it becomes higher with increasing age. It is temporarily raised during muscular or mental work, and falls again during rest. The diastolic pressure is about 40 mm. Hg lower than the systolic.

THE AUDITORY METHOD.—A modification of the above method of measuring arterial blood-pressure in man is the *auditory method*, in which the flow of blood along the artery peripheral to the rubber bag is ascertained, not by feeling the radial pulse, but by listening through a stethoscope to the sounds produced in the brachial artery at the bend of the elbow. The pressure is slowly raised. When the diastolic pressure is just exceeded slight sounds become audible. These sounds, which are synchronous with the heart-beats, increase in intensity as the pressure is raised until they reach a maximum. As the pressure in the bag rises still higher, these sounds become fainter, and they finally cease to be heard when the pressure in the bag (and manometer) is just above the true systolic pressure. The systolic pressure as found by the auditory method is a little higher than that determined by palpation.

VENOUS PRESSURE IN MAN is measured in the following manner: A small glass funnel is placed over a peripheral vein and cemented down to the skin by collodion so as to make an air-tight junction; the funnel-tube leads to a water-manometer and

to a pressure-bulb. Air is blown into the funnel; when the pressure reaches a certain height the vein collapses, and the reading of the manometer represents the venous pressure. The same method, a smaller funnel being used, may be employed to determine *capillary pressure*, the collapse of the capillaries being indicated by blanching of the skin. The capillary pressure varies greatly; recent experiments show that it may be as low as 3 mm., but rarely exceeds 30 mm. Hg. The venous pressure varies from 8 to 10 mm. Hg in the smaller veins; in the large veins near the heart it is only 1 or 2 mm. Hg, and may be negative.

SECTION III

THE PULSE.—If the arterial system consisted of a series of rigid tubes, the blood forced into it from the heart would, in accordance with the laws of hydrostatics, cause a very rapid rise of pressure throughout the whole system, and an equal quantity of blood would at once escape from the distal end of the system. Owing to the fact that the arteries are distensible, only a fraction of the amount of blood entering the arterial system at each systole is forced through the arterioles during the systole, and much of the force of the heart is expended in further expanding the already distended arterial system to accommodate the extra blood sent into it. The expansion of the arteries starts at the root of the aorta, and proceeds as a wave along the whole arterial system, gradually dying away before the capillaries are reached. This wave of expansion constitutes the *pulse*. It travels at a rate of 6 to 8 metres a second, and is independent of the movement of the main mass of blood along the arteries, the velocity of which rarely exceeds half a metre a second.

The pulse can be felt, and often seen, in the superficial arteries of the body, *e.g.* the radial artery. In order to study it more exactly a graphic record may be obtained by means of an instrument known as a *sphygmograph*, of which many forms exist.

Dudgeon's sphygmograph, which is illustrated diagrammatically in Fig. 57, may be

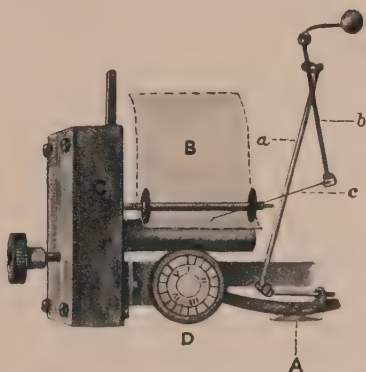


FIG. 57.—Dudgeon's sphygmograph; slightly diagrammatic. Explanation of figure in text.

attached by a band round the wrist in such a way that the small metal plate A rests on the skin over the radial artery. The movements of the arterial wall are magnified by the series of levers *a*, *b*, *c*, and are recorded by the free end of the lever *c*, which writes on a moving strip of blackened (smoked) paper B. The paper is moved by means of a small clockwork arrangement, and the pressure of the plate A on the artery can be adjusted by means of the dial D.

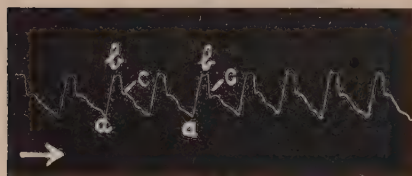


FIG. 58.—Pulse-tracing from the radial artery.

A typical pulse-tracing thus obtained is seen in Fig. 58. It shows a sharp rise from *a* to *b*, succeeded by a steady fall, interrupted at *c* by a small notch which is immediately followed by a slight wave. The rise *a* to *b* constitutes the *primary*, or percussion, wave; the wave following *c* is the *dicrotic* wave, the notch

just preceding it being the dicrotic notch. Other small waves, some preceding the dicrotic wave (pre-dicrotic), and others following it (post-dicrotic), sometimes occur; they are due to slight oscillations of the stretched arterial walls, magnified and distorted by vibrations set up in the sphygmograph.

THE PRIMARY WAVE.—This is caused by the sudden expansion of the artery when blood is forced into it during systole, the form of the wave depending upon the peripheral resistance. After the first abrupt expansion of the arteries, the blood usually escapes through the peripheral resistance more rapidly than it enters the arterial system from the heart, and the dicrotic notch appears especially prominent and low down on the downstroke if, in addition to a low peripheral resistance, there is also an elastic arterial wall and a rather low arterial blood-pressure. Such a pulse is of the soft or *dicrotic* type. When the peripheral resistance is great, and the arterial walls hard, or the arterial pressure high, *e.g.* in old age or in Bright's disease, the flow of blood from the arteries into the capillaries is retarded, so that blood continues to enter the aorta during systole more rapidly than it passes through the arterioles; the arteries therefore continue to expand almost to the end of systole, and the dicrotic wave is situated high up and is not conspicuous.

In the aorta the primary wave begins coincidently with the opening of the semilunar valves and the escape of blood into the aorta, as may be seen in Fig. 59, which gives a simultaneous

record of the endocardiac pressure and of the aortic pressure. Since the wave of expansion travels from the aorta to the peri-

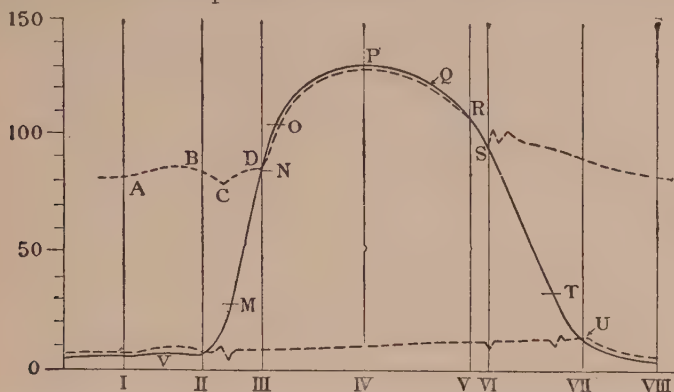


FIG. 59.—The upper dotted curve shows the aortic pressure. The continuous line curve shows the ventricular pressure. The lower dotted curve shows the auricular pressure. (From Wiggers' *The Pressure Pulses in the Cardiovascular System*.)

pheral vessels, the percussion wave begins in the smaller vessels an appreciable time later than in the aorta. This can be readily

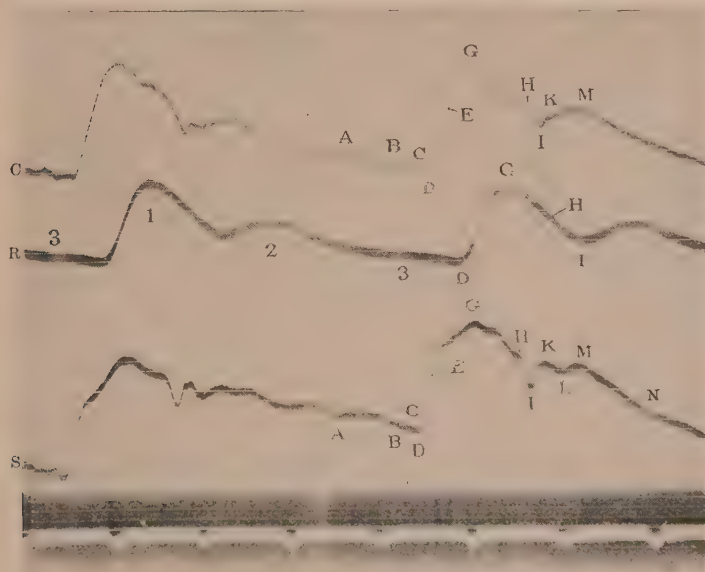


FIG. 60.—C = carotid artery pulse curve. R = radial artery pulse curve. S = subclavian artery pulse curve. (From Wiggers' *The Pressure Pulses in the Cardiovascular System*.)

observed by taking simultaneous pulse-tracings, e.g. one from the subclavian artery, one from the carotid artery, and one

from the radial artery at the wrist. (See Fig. 60.) The tracings are obtained by means of a *polygraph*. A receiver is placed over each artery, and connected with a tambour. The levers are arranged so that one writes directly under the other. The difference in time between the beginning of the percussion waves is measured with the aid of a time-tracing, and distances from the heart of the points on the arteries at which the pulse-tracings are taken are noted; from these data the velocity of the pulse-wave can be calculated. Thus, if the difference in time between the onset of the two pulses is 0.1 second and the difference in their distance from the heart is 0.6 metre, the velocity is 6 metres per second. Normally, it varies from 6 to 9 metres per second. The higher the arterial blood-pressure and the more rigid the arterial walls, the greater the velocity of propagation of the pulse-wave. The length of the wave is from 5 to 6 metres.

THE DICROTIC WAVE.—Fig. 59 also shows that the dicrotic wave occurs immediately after the closure of the semilunar valves, and, as no corresponding wave is present in the endocardiac pressure tracing, the dicrotic wave must have its origin in the arterial system. It was formerly believed that as the primary wave passed along the arteries it was reflected, as a secondary wave, from the obstruction set up wherever the arteries branched, and particularly from the arterioles, where the branchings are very numerous. This small reflected wave, starting at the periphery, was believed to travel back towards the heart as the dicrotic wave. Such a wave is actually produced in an artificial scheme of the circulation where the pulse-wave beats upon a peripheral resistance.

If this view were correct, the distance between the primary and dicrotic waves would naturally be less in the peripheral arteries near the seat of origin of the reflected wave than in the aorta. But the interval between the summits of the primary and secondary waves is of the same length in pulse-tracings taken from the same individual at the same time, whether the artery examined be near, or far from, the heart; for example, it is the same in the subclavian and the femoral arteries. Hence the dicrotic wave must arise at the same point as the primary wave, and, since the primary wave starts at the root of the aorta, the dicrotic wave must start there also. (See Fig. 61.)

It is brought about in the following manner. When the left ventricle ceases to contract, the column of blood travelling along the aorta continues to move in virtue of its momentum, thereby producing a slight fall of pressure at the root of the aorta; and the wall of the aorta shrinks a little. The slight fall of pressure

immediately causes a reflux of blood against the semilunar valves, closing them, and the blood rebounds from the closed valves, thereby producing a small secondary expansion of the aorta; this expansion travels along the arterial system, and forms the dicrotic wave. The height of both the primary and the dicrotic waves is largely determined, first, by the distensibility of the arteries, and, second, by the degree of distension of these vessels between successive heart-beats. If the arteries have become rigid (from old age or disease), their capacity for expansion will obviously be diminished; if they are already greatly distended by a high mean arterial blood-pressure, their capacity for further distension will also be decreased. The conditions most favourable to the appearance of a markedly dicrotic pulse, therefore, are (1) a strongly beating heart, (2) a moderate blood-pressure, (3) highly elastic arteries. These conditions are often very fully realised in young adults during fever.

The rise of pressure caused by the entrance of blood into the arterial system with each heart-beat is greatest where the blood enters the system, namely, at the root of the aorta, and the wave of expansion is largest at this point. Some of this extra pressure is used up in expanding the first section of the aorta, and the force tending to distend the next segment will be slightly less; this process continues from segment to segment along the arterial system, the wave gradually becoming smaller and smaller, until in the capillaries it has entirely disappeared, and no trace of any pulse is visible.

THE PULSE-RATE IN MAN.—The frequency of the heart-beat in any healthy, resting individual is very constant, though

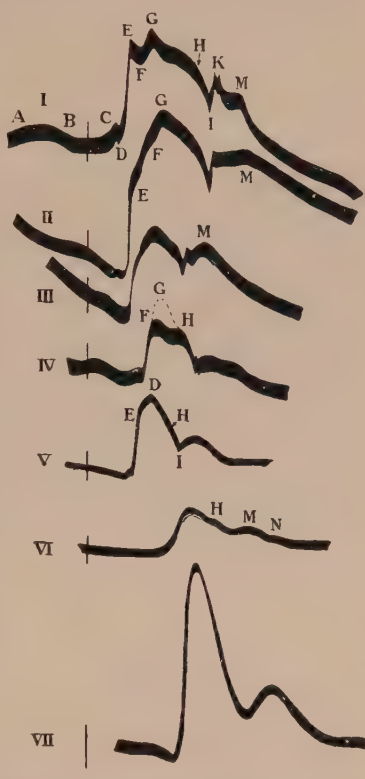


FIG. 61.—I, subclavian artery; II, subclavian artery; III, carotid artery; IV, carotid artery; V, brachial artery; VI, radial artery; VII, femoral artery. (From Wiggers' *The Pressure Pulses in the Cardio-vascular System*.)

the frequency from individual to individual is subject to wide variations. Its average is often said to be 72 per minute in people in middle life. In young adult males the average is about 75, and in young adult females about 80 per minute. Some people, however, normally have a slow and others a frequent pulse, the range of variation in different individuals being between 55 and 90 per minute. Alterations in the pulse-rate are continually taking place in daily life, and are brought about by one or other of the reflex mechanisms just described. The pulse is slightly quickened by the taking of food, and is considerably accelerated by (1) active muscular exercise, (2) emotion, (3) pain; the two latter conditions are often accompanied by muscular movements (unless these are restrained by an effort of the will) and by increased respiratory movements. As a result of the muscular and respiratory movements the inflow of venous blood to the heart may become very large, and the concomitant acceleration of the heart greatly increases its output in a given time, thereby enabling it to send a much larger supply of blood and of oxygen to the various organs and tissues of the body. In this way, acceleration of the heart plays an important part in the adjustment of the circulatory mechanism to the needs of the body.

From infancy to middle life there is a steady decrease in the pulse-rate; in old age again a slight increase.

In health, marked slowing of the pulse-rate is of quite frequent occurrence, particularly in athletes, and is also often observed in pathological conditions.

THE VENOUS PULSE.—This is normally present in the great veins near the heart, and direct observation of the jugular vein shows two visible pulse-waves for each heart-beat. This pulsation, derived from, and corresponding with pressure changes in, the right auricle, is transmitted along the column of blood in the great veins in the opposite direction to the flow of the blood. Normally it is soon extinguished, though in certain abnormal states it travels far enough to impart a palpable pulsation to the liver. In order to record the venous pulse and to interpret it, a simultaneous tracing of the venous pulse and of the radial pulse is obtained by means of the *polygraph* described on p. 128. One cup is pressed on to the skin over the jugular vein just above the clavicle; another receiver is placed over the radial artery at the wrist. Each cup is connected with a tambour attached to a lever and the two levers are arranged to write one above the other.

Fig. 62 represents a tracing of the venous pulse, taken by this method and shows three waves; the first rise, *a*, corresponds with the auricular systole, the second, *c*, is simultaneous with the

beginning of the ventricular systole, and the third, more rounded wave, *v*, is due to the gradual filling of the auricle towards the end of the ventricular systole.

The venous pulse is confined to the large veins, and, as the arterial pulse is extinguished in the arterioles, there is normally no pulsation in the smaller and medium-sized veins. The arterial pulse-wave, may, however, extend into the smaller veins under certain

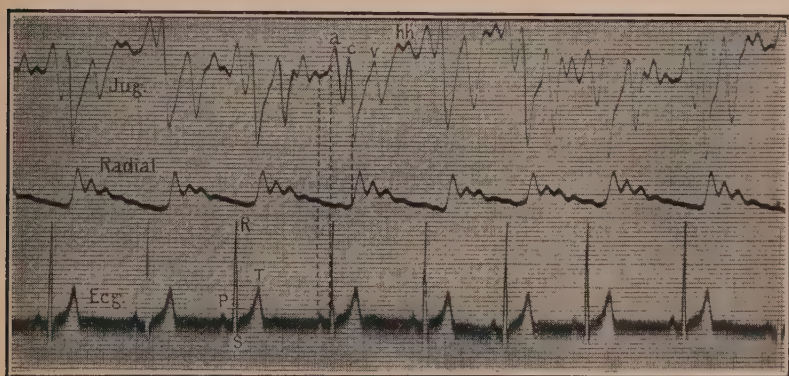


FIG. 62.—Upper tracing = jugular vein ; middle tracing = radial artery ; lower tracing = electrocardiogram.

conditions. When, for example, the chorda tympani nerve is stimulated, the arterioles of the submaxillary gland become dilated, and not only is the amount of blood flowing through the gland increased, but the pulse-wave extends into the veins coming from the gland. The transmission of the pulse into the veins is due, in this and similar cases, to the diminution of the resistance in the arterioles resulting from their dilatation.

SECTION IV

VELOCITY OF THE BLOOD-FLOW.—The rate at which fluid flows along a tube, the bore of which is constant, depends solely upon the amount of fluid entering the tube in a given time. The same principle holds good in the body, and, provided the calibre of the blood-vessels remains unchanged, the *actual* velocity of the blood-stream as a whole is determined by the amount of blood expelled from the heart into the aorta in a given time, that is to say, it depends upon the driving force of the heart-pump. If the heart ceases to beat, the circulation comes to a standstill ; if the heart is beating feebly, very little blood enters the aorta, and the blood flows slowly round the body. If, however, the heart is

beating forcibly and frequently, the velocity of the blood-flow may be considerable. These differences are of importance, since the rate at which oxygen is carried from the lungs to the various tissues of the body is determined by the rapidity of the circulation.

The *relative* velocity of the blood-flow in the arteries, capillaries, and veins is determined solely by the total width of the channels through which the blood is flowing. Since the same quantity of blood has to pass in a given time through each cross-section of the bed of the vascular system, it is obvious that the smaller the cross-section the greater must be the velocity of the blood-flow. For the same reason water flows rapidly in a river where the channel is narrow, and slowly where the channel widens out into shallows.

When an artery divides, each branch is smaller than the parent artery, but the total cross-section of the two branches is larger than that of the parent artery. The total cross-section of the vessels thus increases with each branching, and in the capillaries it has been estimated to be about 800 times as great as that of the aorta. The sectional area of the veins gradually decreases as they unite to form larger vessels, and that of the large veins entering the heart is approximately twice as great as that of the aorta. It has been found that whereas the average velocity of the blood in the large arteries is about 400 to 500 mm. a second, it varies from $\frac{1}{2}$ to 1 mm. a second in the capillaries, and is from 200 to 250 mm. a second in the large veins.

In a small organ, such as the kidney or submaxillary gland, the velocity of the flow of blood is also modified by *local* changes in the arterioles. Dilatation of the arterioles lessens the resistance to the flow of blood through the organ without affecting the general arterial blood-pressure, and since the resistance to the blood-flow is lessened in that organ as compared with other organs in the body, the blood flows through that section of the circulatory system with increased velocity and in larger amount. This result, which furnishes an apparent exception to the general statement made above, occurs only when the organ is so small that alterations in the calibre of its arterioles do not appreciably affect the general blood-pressure.

METHODS OF MEASURING THE VELOCITY OF THE BLOOD-FLOW.—LUDWIG'S STROMUHR.—This consists of two glass vessels, A and B, connected at the top (Fig. 63). On A is a mark *c*, the capacity of the vessel between the mark *c* and the opening *a'* being exactly known. These vessels are fixed at their lower ends into a metal disc H, placed upon a similar disc N, and capable of being rotated upon the latter through two right angles.

The openings a' and b' in the upper disc fit exactly over those (a and b) in the lower disc; from these openings in the lower disc arise two tubes F and G. The experiment is carried out as follows: A clip is placed on an artery; the artery is then divided distally to the clip and one end of it is connected with tube F, the other with tube G. The vessel A, which communicates with the proximal end of the artery, is filled with olive oil up to the mark c , and the remainder of the apparatus is filled with defibrinated blood or saline solution. The blood is then allowed to flow from the artery through F into A, thus driving the oil over into B and

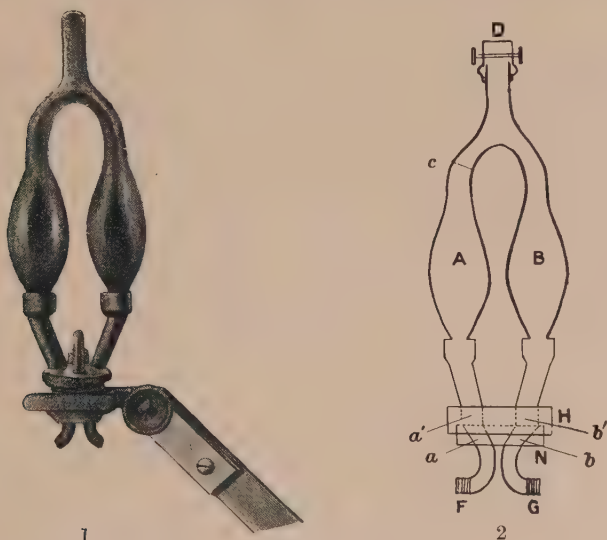


FIG. 63.—1, Ludwig's stromuhr; 2, Diagrammatic representation.

sending the defibrinated blood into the peripheral end of the artery. As soon as the blood leaving the artery reaches the mark c , the disc H is rapidly turned through two right angles, and the blood flowing from the artery now drives the oil back into A. When the oil again occupies its original position, the disc is once more rotated through two right angles. This process is repeated as often as necessary, the experiment being carried on for any desired period; clotting of the blood can be prevented by the previous injection of hirudin into the animal. The diameter of the artery is then measured. From these data the velocity of the blood-flow can be calculated by means of the formula:—

$$\text{Velocity} = \frac{\text{volume (passing through the stromuhr) per second}}{\text{sectional area of blood-vessel}}$$

If the capacity of the bulb up to the mark *c* is 5 c.c., and it was filled six times in a minute, then the amount of blood passing through the instrument would be 30 c.c. in one minute, or $\frac{1}{2}$ c.c. in one second. Supposing the diameter of the artery to be 2 mm., the sectional area is πr^2 , and the rate of flow can be calculated as follows :—

$$\text{Velocity} = \frac{0.5 \text{ c.c.}}{3.1416 \times 1^2} = \frac{500 \text{ c.mm.}}{3.1416} = 159 \text{ millimetres per second.}$$

SECTION V

THE REGULATION OF THE VASCULAR MECHANISM.—

In order that the various tissues of the body may receive an adequate supply of nutritive material and oxygen, it is essential that the blood-supply to the different organs should be varied in accordance with their needs. This end is attained by means of the central nervous system, which can modify the rate of the heart and the calibre of the arterioles in response either (1) to external stimuli, or (2) to impulses arising in the different parts of the body itself, or (3) to changes in the character of the circulating blood. The third factor also directly influences the force of the heart-beat and the calibre of the vessels.

THE VASO-CONSTRICTOR NERVES.—If the ears of a rabbit, preferably a light-coloured one, are examined, it will be observed that when one cervical sympathetic nerve is divided the ear on that side almost immediately becomes flushed. The central artery and its branches can be seen to become wider, many small vessels previously invisible come into view, and the whole ear becomes warmer than the opposite one. Stimulation of the peripheral end of the cervical sympathetic nerve causes an immediate constriction of the blood-vessels, many of which disappear from view, and the ear becomes paler and cooler than that of the opposite side.

This experiment, which was first carried out by Claude Bernard, shows that the cervical sympathetic nerve contains fibres which run to the blood-vessels of the ear, and which, when stimulated, cause constriction of the arterioles by the contraction of their muscular walls. It proves, further, that normally the muscular coats of the arterioles are neither fully relaxed nor fully contracted, but are in a state of partial contraction, which is spoken of as *tone*. The tone of the arterioles exists only so long as they are in connection with the central nervous system, and is

dependent upon impulses passing from the nervous system. The nerve-fibres which carry these impulses to the arterioles, and which, when stimulated, increase their tone, causing them to constrict still further, are called *vaso-constrictor* nerves.

In other organs, the presence of vaso-constrictor nerves, and the effect of section or stimulation of these nerves on the calibre of the arterioles has been ascertained, not by direct ocular observation, but by determining the amount of blood flowing through the organ in a given time. The volume of blood (V) flowing through an organ in a given time varies directly with the mean arterial pressure (P) and inversely with the resistance (R) in its arterioles, and is represented by the formula $V \propto \frac{P}{R}$. The arterial

pressure tends to drive blood through the organ, whereas the resistance offered by the arterioles tends to lessen the amount of blood entering the organ. Hence the rate of blood-flow through a small organ, such as the kidney, may be altered in one of two ways. On the one hand, in the absence of any active change in its arterioles, a rise of the general arterial blood-pressure will force more blood through the arterioles of the kidney. On the other hand, if the mean arterial pressure remains constant, dilatation of the renal arterioles will lead to an increased rate of blood-flow through the kidney by lessening the resistance to the flow of blood. In experiments on the rate of blood-flow through an organ it is necessary, therefore, to record both the rate of flow and the mean arterial pressure, in order to ascertain whether the alterations in flow are due to local changes in the arterioles, or to changes in the general arterial pressure, or possibly to a combination of these factors.

THE PLETHYSMOGRAPH.—The amount of blood flowing through an organ in a given time may be directly measured by allowing the blood escaping by the veins to pass along a graduated tube. Thus if 2 c.c. of blood flow into the tube in four seconds, the rate of flow is 30 c.c. per minute. This method is very useful in the case of small organs, such as the kidney or the submaxillary gland.

Changes in the calibre of its arterioles affect not only the rate at which blood flows through an organ, but also the amount of blood present in it, and hence its volume, at any moment. For its example, constriction of the arterioles of an organ lessens both volume and the rate of the blood-flow through it. Consequently, alterations in the rate of the blood-flow through an organ can be indirectly ascertained by recording the variations in its volume. For this purpose the following method is employed. The organ

is placed in an air-tight box, known as a *plethysmograph*, provided with a small opening which is connected with a piston-recorder arranged to write on a drum (Fig. 64). When the organ expands,

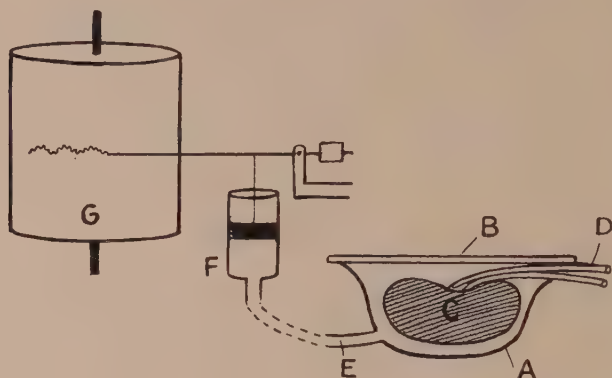


FIG. 64.—Method for recording changes in the volume of an organ (the plethysmograph).

A, oncometer, in which lies the kidney C. D, renal vessels. B, glass lid.
F, piston recorder. G, revolving drum.

the air in the box is driven along the tube into the piston-recorder, thereby raising the lever; shrinkage of the organ has the opposite effect. The form of plethysmograph varies with the shape of the organ which is being studied. The one generally used for the kidney, and known as an oncometer (Fig. 65), is made of

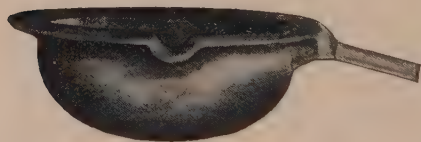


FIG. 65.—Oncometer.

dental wax and has a glass lid; in one side is a groove through which the renal vessels and nerves can pass. The box is made air-tight by filling the interstices with vaseline. Fig. 66 represents a record of the

volume of the kidney thus obtained, simultaneously with a general blood-pressure tracing, and shows the effect of stimulating the peripheral end of a divided renal nerve.

By one or other of these methods it is found that division of the nerves passing to the kidney produces an increase of its volume and a larger flow of blood through it, whereas stimulation of the nerves has the opposite effect. Since in these experiments the general arterial pressure remains practically unaltered, the changes in the blood-flow produced by section or stimulation of the renal nerves must be brought about by alterations in the calibre of the arterioles of the kidney.

THE VASO-MOTOR CENTRE.—Experiments of this kind show that the arterioles of almost every organ in the body are supplied with vaso-constrictor nerves. The tone of these vessels

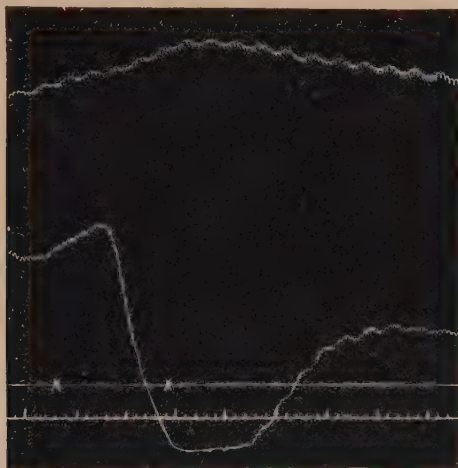


FIG. 66.—Tracing of arterial blood-pressure (1), and kidney-volume (2). Between X and X the 10th anterior thoracic nerve-root was stimulated, causing a decrease in kidney-volume. (From *Practical Physiology*, by Pembrey and others.)

is controlled by a centre, the *vaso-motor centre*, lying in the medulla oblongata ; nerve-fibres pass from the cells of this centre down the spinal cord to end, in all probability, round cells in the lateral horn in the thoracic region, and round corresponding cells in the lumbar region. These cells give off small medullated fibres, which leave the spinal cord by the anterior roots and enter the white rami communicantes to form part of the sympathetic system. From this branches are given off to the vessels of the tissues.

The mean arterial pressure depends largely upon the resistance offered by the arterioles to the flow of blood through them ; it rises when they are constricted, and falls when they are dilated. Hence stimulation of the vaso-motor centre, by causing constriction of arterioles all over the body, produces an enormous rise of blood-pressure ; destruction of the centre is followed by dilatation of the arterioles, and the blood-pressure falls to 50 mm. Hg, or less. The centre lies in the floor of the fourth ventricle, its lower limit in the rabbit being about 4 mm. above the apex of the calamus scriptorius and its upper limit about 4 mm. higher. Its position has been ascertained experimentally by observing the effect on the blood-pressure of transection of the brain-stem at

various levels. Section through the pons or upper part of the medulla oblongata does not affect the blood-pressure; when the section passes through the upper end of the centre it produces a slight fall of pressure, and if a section is made a few millimetres lower the fall of pressure is maximal. On division of the spinal cord in the cervical region, all the arterioles are cut off from the vaso-motor centre in the medulla, and the fall of blood-pressure is as great as after destruction of the centre itself. When the transection is made in the thoracic region, only those arterioles which receive vaso-constrictor nerves from the spinal cord below the lesion will lose their tone; and the fall of arterial pressure becomes less marked the lower the level at which the spinal cord is divided. Thus transection in the lower lumbar region has little effect upon the mean arterial pressure.

THE SPINO-MOTOR CENTRES.—If an animal is kept alive for some hours or days after transection of the spinal cord, its arterioles gradually recover their tone and the blood-pressure returns to a normal level. This is brought about by means of subsidiary vaso-motor centres in the spinal cord. These spinal vaso-motor centres probably play an important part in maintaining the tone of the arterioles. Normally they are subjugated to the control of the main centre in the medulla. The constant activity of these centres is largely maintained by the stimulus provided by the presence, in the blood, of carbon dioxide (p. 189). On destruction of the spinal cord the blood-pressure falls almost to zero.

THE CORONARY VESSELS.—The only arterioles in the body which are not known to be influenced by vaso-constrictor nerves are the cerebral and coronary vessels. The existence of vaso-constrictor nerve-fibres supplying the smaller pulmonary vessels has been demonstrated by means of adrenaline. This substance stimulates the endings of the vaso-motor nerves in the walls of the arterioles, and thus produces the same effect upon the arterioles as does stimulation of the nerves themselves. It follows, therefore, that, if the addition of adrenaline to the blood flowing through an organ brings about constriction of its arterioles, the blood-vessels of that organ must be supplied with constrictor nerve-fibres. Observation has shown that, when the lungs are perfused with blood under a constant pressure, the addition of adrenaline to the blood lessens the outflow from the lungs owing to constriction of the pulmonary arterioles. Hence it may be concluded that vaso-constrictor fibres are distributed to the pulmonary vessels.

THE VASO-DILATOR NERVES.—In many parts of the body the arterioles are supplied not only with vaso-constrictor but also with vaso-dilator nerves, stimulation of which produces dilatation of the vessels owing to relaxation of their muscular walls. The chorda tympani nerve, for example, carries vaso-dilator fibres to the vessels in the submaxillary gland, and when it is stimulated the blood-flow through the gland is increased, and may become four or five times as large as that taking place before stimulation of the nerve. Since the general blood-pressure remains unaltered, the increase in the blood-flow through the gland must be due to dilatation of its arterioles. Vaso-dilator fibres are also found in the nerves supplying the other salivary glands, the tongue, and other structures in the head. Similar fibres leave the spinal cord by the anterior roots of the second and third sacral nerves; and stimulation of these nerves, which are called the *nervi erigentes*, causes dilatation of the blood-vessels of the generative organs and of the rectum.

The vaso-dilator nerves show two important points of difference from the vaso-constrictor nerves. In the first place, mere section of the nerves produces no obvious effect upon the calibre of the blood-vessels, so that, unlike the vaso-constrictors, the vaso-dilator fibres do not appear to exercise a continuous influence upon the tone of the arterioles. In the second place, the cell-stations for these nerves lie, not in the sympathetic ganglia, but close to, or even within, the organ whose arterioles they supply.

In the instances just given, the nerves contain only vaso-dilator fibres, but in the nerves supplying the limbs both vaso-dilator and vaso-constrictor fibres are present. Stimulation of the peripheral end of a nerve, such as the sciatic, usually causes vaso-constriction, though the existence of vaso-dilator fibres can be demonstrated in one of the following ways :—

(1) If the sciatic nerve is divided and its peripheral end stimulated immediately, the arterioles become constricted, but when the nerve is stimulated two or three days after section the arterioles dilate. This result is due to the fact that the constrictor fibres degenerate, and cease to carry impulses, earlier than do the dilator fibres.

(2) If the sciatic nerve is stimulated with single induction shocks repeated at intervals of one or two seconds, these shocks stimulate only the dilator fibres, and the arterioles dilate.

(3) The dilator nerves are excited more readily than the constrictor nerves by mechanical stimuli, such as pinching the nerve.

(4) If a limb is cooled, stimulation of the nerve to that limb is followed by dilatation of the arterioles.

The change in the calibre of the arterioles thus produced leads to a corresponding alteration in the amount of blood flowing through the vessels of the limb, and alters the volume of the limb. These changes in volume can be readily recorded by enclosing the distal part of the limb in a plethysmograph of suitable shape, which is connected with a volume (*e.g.* piston) recorder.

Bayliss has shown that the vaso-dilator fibres to the limbs leave the spinal cord by the posterior roots, and that stimulation of the peripheral end of a posterior root causes marked dilatation of the arterioles, and therefore an increase in the volume of the limb (Fig. 67). The posterior root fibres starting in the skin and

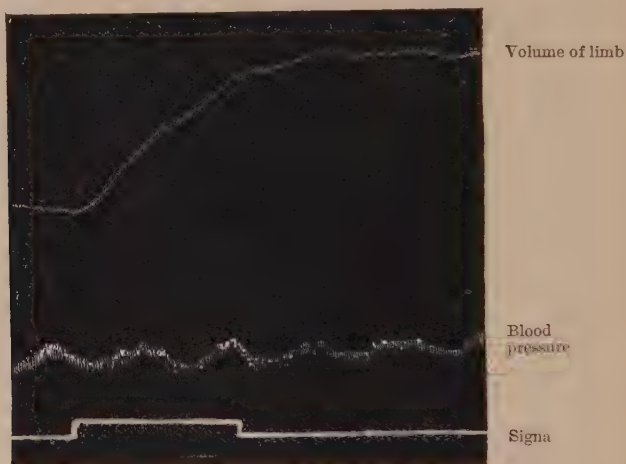


FIG. 67.—Stimulation of peripheral end of 7th lumbar posterior root. (Bayliss.)

deep tissues normally carry impulses from these structures to the spinal cord and brain. When stimulation of the peripheral end of the posterior root causes dilatation of the arterioles, the impulses must pass towards the periphery, that is, in the opposite direction to that taken by the impulses from the skin. For this reason the impulses running towards the periphery and causing vaso-dilatation have been called *antidromic*.

AXON-REFLEXES.—In normal circumstances a stimulus applied to the skin at A (Fig. 68) will give rise to an impulse passing along the sensory nerve B into the spinal cord; in its course each nerve-fibre gives off a collateral branch C, which ends in the wall of an arteriole D of the limb. The impulse passing along the fibre B also passes along the collateral C to the arteriole

D, and causes it to relax. Since nerve-fibres can conduct impulses in both directions, stimulation of the posterior root fibres at E gives rise to an impulse which, travelling down the nerve, passes by the collateral branch C to the arteriole D, and causes it to relax. We see, therefore, that whether the stimulus is applied at the periphery A or at E, the impulse reaches the arteriole along the branch C. The effect of stimulation at A, which is not a true reflex, is called an *axon-reflex*. If the fibres of the posterior root become degenerated peripherally to the ganglion, the axon-reflex disappears, and a stimulus applied to the skin at A causes no dilatation of the subcutaneous vessels.

This axon-reflex is of great importance to the body. As is well known, an irritant (*e.g.* a mustard plaster) applied to the skin causes it to become red owing to dilatation of the cutaneous

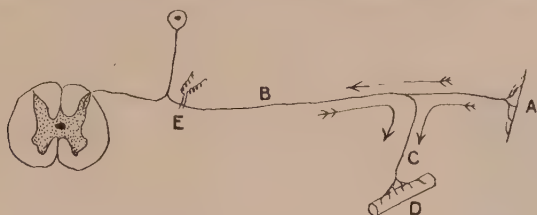


FIG. 68.—Scheme to show path of antidromic impulses (axon-reflex).

vessels. The dilatation of the vessels is one of the means by which the tissues protect themselves against injuries or irritants, and if the vascular changes fail to occur owing to degeneration of the peripheral sensory fibres, the damage done by the irritant to the tissues may be much more severe.

Vaso-dilator fibres are also present in the sympathetic system itself, although their presence is not readily demonstrated owing to the greater abundance of vaso-constrictor fibres; but when the endings of the latter are paralysed by the drug ergotoxine, stimulation of the splanchnic nerves causes vaso-dilatation and a fall of blood-pressure. Whereas the vaso-constrictor fibres, controlled by the vaso-motor centre, regulate the tone of the arterioles of the body as a whole, the vaso-dilator fibres bring about an increased flow of blood in individual organs. They probable do this by a local production of a substance of a histamine-like character (Lewis).

SECTION VI

INFLUENCES AFFECTING THE VASO-MOTOR CENTRE.—

The vaso-motor centre is extremely susceptible both to impulses reaching it from other parts of the nervous system, whether these

come from the higher parts of the brain or through the peripheral nerves, and to changes in the character and amount of the blood passing to the brain. Its activities are constantly varying in response to these stimuli in such a way that the mean arterial pressure is raised to meet special needs of the body, and is prevented from falling below the level necessary for the adequate supply of blood to the tissues and more especially to the brain.

NERVOUS STIMULI ON VASO-MOTOR CENTRE.—The depressor nerve is a purely afferent nerve, originating in the root of the aorta, and passing to the brain. Electrical stimulation of its central end causes (1) a fall of blood-pressure, and (2) a decrease in the rate of the heart. After section of the vagus nerves, stimulation of the depressor nerve does not affect the rate of the heart, though it still produces a fall of blood-pressure (Fig. 69),

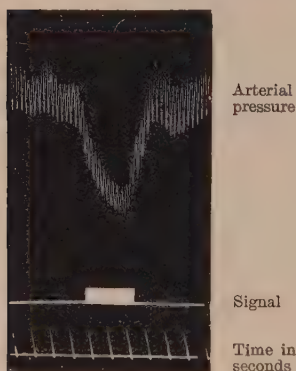


FIG. 69.—Tracing showing the effect upon the blood-pressure of stimulating the depressor nerve. (From Bayliss' *Principles of General Physiology*.)

which in these circumstances must be due to dilatation of the arterioles. The dilatation is brought about by lessening the activity of the vaso-motor centre and by decreasing the tone of the arterioles. It is a reflex act, the afferent path being the depressor nerve. In all probability, when the arterial blood-pressure is very high, impulses are set up in the endings of the nerve in the stretched aortic wall which reflexly lower the blood-pressure, and thus lessen the strain placed upon the heart.

Increased activity of the centre and a rise of blood-pressure are brought about by stimulation of most sensory nerves, and also by impulses passing to the centre from the cerebral cortex during muscular exercise and in violent emotional excitement, such as fear or anger.

COMPOSITION OF THE BLOOD ON THE VASO-MOTOR CENTRE.—The vaso-motor centre is extremely sensitive to changes in the composition of the blood supplying it, being stimulated by a lack of oxygen or by the presence of an excess of carbon dioxide in the blood. The effect of lack of oxygen, and of excess of carbon dioxide, is seen in its most extreme form in asphyxia (p. 191), but even a slight excess of carbon dioxide

stimulates the centre and leads to constriction of the arterioles and a rise of arterial pressure. The same effect is produced by the injection into the blood-stream of small amounts of an acid, such as lactic acid, because acids set free carbon dioxide by decomposing the bicarbonate of the plasma. Conversely, reduction of the carbon dioxide content of the blood by abnormally deep and rapid respiration leads to depression of the vaso-motor centres, and the blood-pressure quickly falls to a low level (p. 189). In this condition, known as *acapnia*, there is often dizziness owing to inadequate circulation in the brain. The blood thus depleted of carbon dioxide, is more alkaline than normal, because the ratio $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$ in the blood-plasma is reduced (p. 73); but this alkalinity cannot be the cause of the depression of vascular tone, because if the blood be rendered more alkaline by the injection of sodium bicarbonate instead of by withdrawal of carbon dioxide, no such fall of blood-pressure is seen. Hence it is concluded that carbon dioxide is in itself a specific excitant of the vaso-motor centres, and its presence in the blood is largely responsible for their normal tonic action. The vaso-motor centre is stimulated whenever the amount of blood passing through the brain in a given time diminishes.

TRAUBE-HERING CURVES.—During asphyxia the blood-pressure tracing sometimes shows, in addition to the oscillations caused by the heart-beat and respiration, other waves much slower in rhythm and larger in amplitude than the respiratory waves. These waves, known as *Traube-Hering curves*, are brought about by slow rhythmic variations in the activity of the vaso-motor centre. Their occurrence also after severe hæmorrhage suggests that the activity of the vaso-motor centre assumes a rhythmic character as the outcome of an inadequate supply of oxygen.

The subsidiary vaso-motor centres, like the chief centre, are also sensitive to chemical stimuli, and although probably they take little part in the vascular changes normally occurring in the body, their activity can be excited by asphyxia, or depressed in *acapnia*.

THE SPLANCHNIC AREA.—In whatever way the activity of the vaso-motor centre is increased or lessened, the resulting constriction or relaxation of the blood-vessels is most pronounced in the abdominal organs. The splanchnic nerves send constrictor fibres to the blood-vessels of almost the whole of the abdominal viscera, and the total capacity of these vessels is so large that the

amount of blood contained in them forms a great proportion of the total blood in the body. Further, the general arterial pressure is more markedly altered by section or stimulation of the splanchnic nerves than of any other nerve in the body.

When the arterioles of the abdominal organs become constricted in response to stimulation of the splanchnic nerve, the splanchnic viscera naturally contain less blood than before, and more blood has to be accommodated in other parts of the vascular system. As a consequence the large and medium-sized arteries are more fully distended with blood, and in this way the general arterial blood-pressure is raised. Constriction of the arterioles of the abdominal organs thus leads to a rise of blood-pressure in two ways, (1) by the increased peripheral resistance, and (2) by the diminished capacity of these vessels to contain blood; the first of these is the more important.

Hence the maintenance of the mean arterial pressure at a constant level, in spite of the varying influences which are brought to bear upon the vaso-motor centre in daily life, is largely effected by changes in the degree of constriction of the arterioles supplied by the splanchnic nerves and constituting the *splanchnic area*. For example, when the depressor nerve is stimulated, the fall of pressure which occurs is due mainly to the dilatation of the arterioles in the splanchnic area. When the blood-supply to the vaso-motor centre is deficient, the resulting rise of blood-pressure is caused primarily and chiefly by constriction of the arterioles of the abdominal organs. When during muscular exercise an increased flow of blood through the skeletal muscles is required the vessels in the splanchnic area are constricted, consequently more blood is diverted into the muscular system. On the contrary, during digestion the organs require an abundant blood supply; the vessels of the skin are constricted, while the arterioles of the digestive tract are relaxed. It is for this reason that severe exercise taken immediately after a meal tends to disturb digestion.

SECTION VII

INFLUENCE OF GRAVITY ON THE CIRCULATION.—If a thin-walled cylindrical rubber bag is filled with fluid and held with its long axis vertical, the fluid, under the influence of gravity, tends to accumulate at, and to distend, the lower end of the bag. In the body also, the blood tends to accumulate in the most dependent parts, and if a rabbit is held up by the ears the blood accumulates in the abdominal area, particularly in the large veins,

and the arterial blood-pressure falls (Fig. 70). As a result, the amount of blood passing through the brain in a given time is inadequate and its functions are seriously interfered with, so much so that it is said to be possible to kill a hutch rabbit by holding it up in this position for a short time, death being due to anæmia of the brain.

The influence of gravity is antagonised completely in man, and to a lesser extent in most animals, by means of a compensating action on the part of the vaso-motor centre. When a man

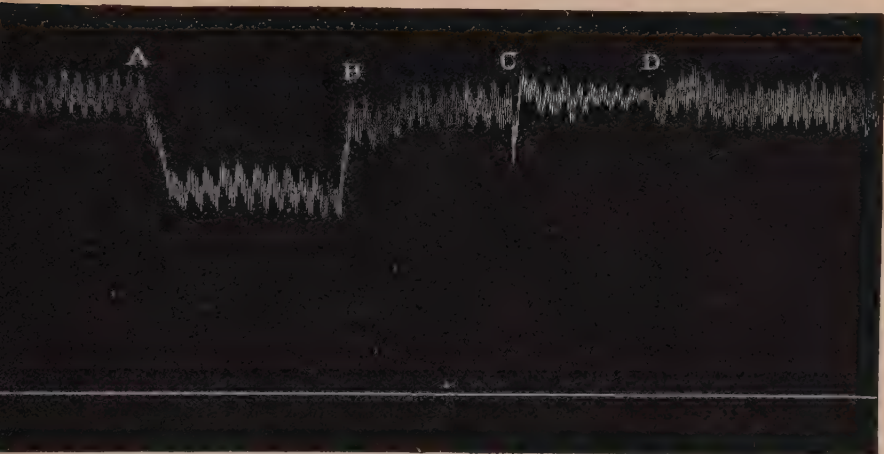


FIG. 70.—Aortic blood-pressure of a dog. Effect of posture. (L. Hill.)
(From *Practical Physiology*, by Pembrey and others.)

A-B, vertical, head up; B, horizontal; C, vertical, head down; D, horizontal.

rises from the horizontal to the standing position, the blood tends to accumulate in the abdomen, and the supply of blood to the brain is diminished. This diminution at once stimulates the extremely sensitive vaso-motor centre, which sends out impulses constricting the arterioles of the splanchnic area, thereby forcing the blood out of this area into the rest of the body, including the brain. Conversely, the splanchnic arterioles relax to some extent whenever an individual changes from the vertical to the horizontal position.

THE REACTION OF THE VASO-MOTOR CENTRE to any change in the position of the body as regards gravity is so rapid and complete that we are not normally aware of its existence. The temporary giddiness, which is often noticed by individuals who are anæmic or in poor health, on changing suddenly from a horizontal to a standing position, is due to the fact that the

response of the vaso-motor centre to the change of position is slower than usual, and that for a few moments the brain is inadequately supplied with blood. In the same way "fainting" is in many cases caused by temporary diminution of the activity of the vaso-motor centre, so that the blood-pressure falls and the blood-supply to the brain is deficient, causing loss of consciousness. The compensating action of the vaso-motor centre for the effect of gravity is also inefficient in anæsthetised persons.

In the horizontal position the pressure in the brachial and femoral arteries is almost the same, but, owing to the influence of gravity, the arterial pressure in the femoral artery of an individual in the erect position is much higher than that in the brachial artery. The constriction of the arterioles of the legs, however, is so great that the pressure in the capillaries and veins of the leg and foot is no higher than that in the hands. The flow of blood from the foot and leg back to the heart against the force of gravity is greatly assisted, and indeed made possible, by muscular movement; each muscular movement squeezes the blood along the veins towards the heart, and the valves prevent any reflux. In persons who are habitually compelled to stand for any length of time, or in whom the valves are defective, blood tends to accumulate in the veins of the legs, and the veins are apt to become dilated and varicose.

THE EFFECT OF HÆMORRHAGE.—Any considerable loss of blood from the body lessens the amount present in the vascular system, and the output of the heart at each beat decreases; the arterial pressure falls, and the supply of blood to the brain becomes inadequate. The vaso-motor centre is at once stimulated, causing increased constriction of the arterioles; at the same time fluid passes from the tissues into the blood, and the arterial pressure rapidly regains its normal level. After a very severe hæmorrhage these compensatory mechanisms are inadequate, and the blood-pressure remains low.

THE INFLUENCE OF ADRENALINE.—The structure and functions of the suprarenal glands are dealt with in Chapter XXII, but it is necessary to mention at this point their influence on the circulation. These glands produce a substance, adrenaline, which can be extracted from them and obtained in a pure form. A minute amount of adrenaline (*e.g.* 0·01 or 0·02 mgr.), injected into a vein, stimulates the nerve-endings of all the fibres of the sympathetic system, including those which supply the arterioles, and causes extreme constriction of all the arterioles except the coronary vessels, which are dilated, and the cerebral vessels, which are

unaffected ; and if the vagus nerves have been divided, a rise of arterial pressure is produced. The suprarenal glands receive fibres from the splanchnic nerves, and, when a splanchnic nerve is stimulated, some of the adrenaline present in the suprarenal gland passes into the suprarenal vein and so into the blood-stream, giving rise to the effects just described.

It is clear, therefore, that, whenever a splanchnic nerve is stimulated, the ensuing rise of blood-pressure is partly due to the increased peripheral resistance brought about by the direct action of the splanchnic nerve on the abdominal blood-vessels, and is partly caused by the constriction of arterioles all over the body by the adrenaline set free into the blood-stream. The influence of these two factors is seen in the form of the blood-pressure tracing, which often shows, as it rises, a small notch or

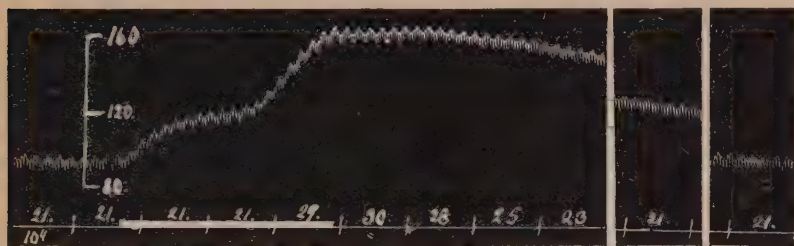


FIG. 71.—Arterial blood-pressure tracing, showing effect of stimulation of left splanchnic nerve. (Anrep.)

step (Fig. 71) ; the first part of the rise is due to constriction of the abdominal blood-vessels, the rise above the notch is due to adrenaline. Owing to the setting free of adrenaline, stimulation of a splanchnic nerve may cause diminution in the volume of the limbs. These effects are produced not only when a splanchnic nerve is divided and its peripheral end is directly stimulated, but also when the impulse passing along the splanchnic nerve originates in the vaso-motor centre itself, as in asphyxia. After extirpation of the suprarenal glands, adrenaline can no longer be set free into the blood-stream, and stimulation of a splanchnic nerve causes a much smaller rise of blood-pressure ; the vaso-constriction is limited to the abdominal vessels, and the blood-vessels of the limbs are passively dilated by the higher arterial pressure (Fig. 72). Adrenaline exerts a variable effect on the capillary tonus, some capillaries being constricted, some dilated, and others unaffected.

LOCAL CHANGES IN THE ARTERIOLES.—The variations in the activity of the vaso-motor centre, brought about by the means

already described, are chiefly directed to regulating the mean arterial pressure and to providing an efficient supply of blood to the brain. Alterations in the calibre of the arterioles in any one organ of the body, as distinct from the body in general, can also be brought about by vaso-dilator nerves, as, for example, the chorda tympani. There is, however, another factor of great importance.

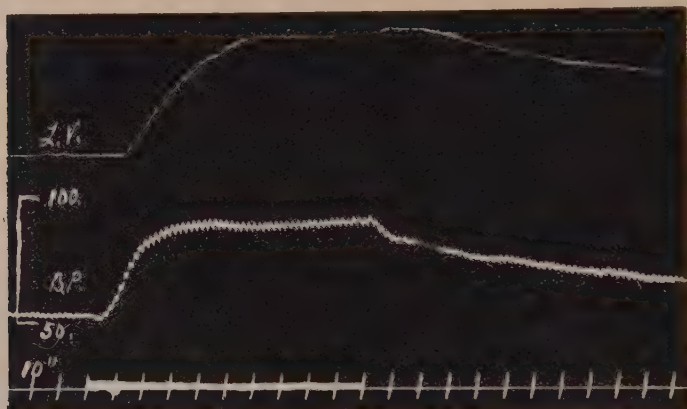


FIG. 72.—Stimulation of a splanchnic nerve after removal of the suprarenal glands. (Anrep.)

L.V., volume of leg enclosed in a plethysmograph; B.P., arterial blood-pressure.

Generally speaking, increased functional activity of any organ of the body is accompanied by dilatation of its arterioles and an increased flow of blood through it; this is brought about by the direct action upon the walls of the arterioles of the waste products (metabolites) formed by the organ during its activity. These include carbon dioxide, lactic acid, and probably other substances, and experiment has shown that, when they are added to the blood passing through an organ, *e.g.* the heart or skeletal muscle, its arterioles dilate.

THE CEREBRAL CIRCULATION.—The circulation of the blood through the brain is peculiar in two respects. In the first place, the brain is enclosed in a rigid case, the skull, which it almost completely fills, and, in the second place, there is at present no conclusive evidence that the arterioles of the brain are under the control of the vaso-motor centre, although the existence of nerveplexuses round them has been observed histologically. The presence of cerebro-spinal fluid in the skull allows for a slight increase in the volume of the blood in the cerebral blood-vessels, since a rise of pressure within these vessels distends them to a

certain extent, and forces some of the cerebro-spinal fluid out of the skull into the sheaths of the nerve-trunks. Apart from this increase, which amounts to only 2 or 3 c.c., the amount of blood in the cerebral vessels cannot be increased, since the capacity of the skull is constant, and the brain which, together with the blood-vessels, practically fills it, is incompressible.

Any increase or decrease in the amount of blood supplying the brain is brought about entirely by variations in the *velocity* with which the blood flows through the cerebral vessels. It has already been pointed out that, if the width of the bed through which the blood is flowing remains constant, the velocity of the flow will vary directly with the pressure which tends to drive the blood along the vessels. In the body this pressure is the mean arterial pressure, and, since the volume of the cerebral vessel remains constant, the velocity of the flow of blood through them will depend entirely on the arterial pressure, provided there is no obstruction to the escape of blood from the cerebral veins. If the arterial pressure rises, the arteries become rather more distended and occupy more space, and, as the total volume of the cerebral vessels remains unaltered, expansion of the arteries must be accompanied by narrowing of the capillaries and veins. The narrowing is not sufficient to cause any obstruction to the escape of blood through these vessels, and the amount of blood flowing through the brain is greatly increased. If the general arterial pressure falls, the velocity of the blood-flow through the brain diminishes, and the amount of oxygen reaching it in a given time is correspondingly decreased. When the supply of oxygen falls, the vaso-motor centre is stimulated, causing constriction of the splanchnic arterioles, and thereby raising the blood-pressure to such a level that the flow of blood through the brain is again sufficient to provide an adequate supply of oxygen. Thus the blood-supply to the brain is modified almost entirely by factors outside the brain itself, being increased whenever the abdominal vessels are constricted, and diminished when these dilate. This constriction or dilatation is effected by the vaso-motor centre in the manner just described.

If the blood-supply to the brain becomes inadequate, the respiratory centre is also stimulated, and the increased respiratory movements bring more blood to the heart, thereby enabling it to expel more blood at each beat and thus to assist the vaso-motor centre in raising the blood-pressure.

The pressure of the cranial contents upon the wall of the skull is just below that within the capillaries of the brain. It cannot be greater than the capillary pressure, since, in these circumstances, the capillaries would collapse and the flow of blood through the

brain would cease. The intra-cranial pressure can be raised by any obstruction to the escape of blood from the cerebral veins, or by the presence within the skull of a foreign body, such as a blood-clot. In the latter case the pressure within the skull may rise sufficiently to compress the capillaries, or even actually to obliterate them. Such compression, which inevitably diminishes the blood-supply to the brain, may cause loss of consciousness and other serious symptoms.

CHAPTER VII

CAPILLARIES AND LYMPH

SECTION I

THE HISTOLOGY OF THE CAPILLARIES.—The capillaries are relatively short vessels having a very fine lumen. The cells forming their walls are only one layer thick. They are flat, plate-like, endothelial cells, united by cement substance which stains with silver nitrate. In developing capillaries the cell outlines are not well seen. The cells of the whole wall take up the stain instead.

The ability to contract was for many years denied to the capillaries on the ground that these flattened endothelial cells, being continuous with those which line the arteries and veins, are non-contractile. Recently, however, their contractility under the influence of chemical substances, changes of temperature, nerve stimulation and the like, have been proved beyond any doubt, and the question that has to be answered is, therefore: Is this observed contractility due to the contractile power of the endothelial cells themselves, or to some other specialised cells? Physiologists are, at the present time, divided in their opinions. Some hold that there are, here and there along the length of the capillary, specialised Rouget cells which encircle the bore of the capillary much like a ring does a serviette. They may be demonstrated by staining with methylene blue *intra vitam*. The protoplasm of the cells is said to be fibrillar. It is claimed that these cells have been observed in active contraction and that they are modified smooth muscle cells, similar to those which form the muscle coats of the smaller arteries. In fact it is authoritatively stated that the bands of muscle seen in the finer arteries gradually thin out, become separated into short rings, and finally are seen here and there as Rouget cells, embracing the capillary wall. Other physiologists, notably Clark, regard these cells as non-contractile. He claims them to be connective-tissue cells. If these cells have been seen to contract, or if constricting bands produced by these cells have been seen round the capillary,

he regards them as being connective tissue and as contracting once and for all, never undergoing a subsequent relaxation such as would be permitted if the cells were muscular in type. The contractility of the capillary walls must then be due to their own endothelium. Time alone will decide which of these two ideas is the correct one.

So far as the ability of the capillaries to change the interior diameter of their bore is concerned, there can be no question. Their diameter varies from one so small that red corpuscles are unable to pass down, to a size which is so large that many red blood-corpuscles can lie side by side in the lumen. With this increase in bore there is always the appearance of stomata or small openings between the endothelial cells. Through these, stomata fluid can pass readily, so also can actively motile white blood-corpuscles. The diffusion of lymph from the circulating blood-fluid into the tissue spaces, which is called lymph formation, depends not alone on diffusion through the endothelial cells of the capillaries, but is also caused by the filtration of fluid through these small stomata. Possibly we are justified in differentiating between the events taking place in an undilated capillary, which is still capable of allowing red blood-cells to pass through it, and one which is widely dilated. In the former, the stomata being occluded, diffusion is depended on for the transference of food substances to the tissues and substances metabolised from them. On the other hand, when the capillaries are dilated and the stomata large, filtration becomes the more important phenomenon.

The lengths of the capillaries vary from about 0.4 to 1 mm. The rate of flow of liquid varies enormously. It may be so slow that, practically speaking, no fluid passes at all, or it may be so fast that a red blood-cell travels at a rate of about 1 mm. per second.

The numbers of the capillaries vary greatly in different tissues. In most tissues they are wonderfully abundant. As Krogh has remarked, a fragment of muscle the diameter of a pin may contain as many as seven thousand parallel capillaries all conveying blood. This very fine subdivision causes the blood to present a very large surface to the tissues: 1 c.c. of blood is spread over an area of about 1 square metre.

EVIDENCE FOR CONTRACTILITY.—Since for many years the active contractile power has been denied to the capillary wall, it will be well to describe one modern experiment which conclusively proves the existence of this power.

The drug urethane, which has no effect on arterioles, brings about dilatation in capillaries when a dilute solution of it is

painted over the sheet of tissue under examination. A further piece of evidence is obtained from the fact that, if the capillaries are found to be contracted, arterial and venous pressures as high as 80 mm. Hg do not force them to dilate. On the contrary, if the capillaries are relaxed, they fill with great readiness either by their arterial or their venous ends.

SECTION II

THE FUNCTIONS OF THE CAPILLARIES.—The function of the capillaries is in the first place to spread a given volume of blood out in such a way that it presents a very large slow-moving surface to the tissues. The endothelial wall being thin, diffusion can very easily take place between the blood in the capillary and the tissue fluid outside it. Thus, oxygen at a comparatively high pressure inside the red blood-cells in the capillaries, diffuses out of the red cells into the lumen of the capillary, then diffuses through the capillary wall into the tissue spaces outside, and lastly, diffuses from the tissue spaces into the surrounding cells, the cause of this diffusion being oxygen “gradient,” each tissue being at a higher oxygen tension than the one succeeding it. In the contrary manner, the carbon dioxide gradient is highest at the tissue and diminishes towards the blood. In addition, as pointed out above, the capillaries have the important function of controlling, by variations in the size of the stomata between their cells, the volume of lymph which is allowed to filter into the tissue spaces.

NERVE-SUPPLY OF CAPILLARIES.—This is probably via the sympathetic, as the following evidence shows.

(1) Stimulation of the sympathetic causes capillary constriction; this still takes place in an animal from which the heart has been removed, or one in which the peripheral arterioles have been blocked up by starch grains. The capillary constriction is not, therefore, a passive change caused by a change in some other part of the circulation.

(2) Interruption of the sympathetic fibres, *e.g.* by extirpation of some of the ganglia, causes a prolonged dilatation of the corresponding area of capillaries. Krogh has shown that capillary tone begins to return about three months later.

(3) Dilatation of capillaries (and arterioles?) follows stimulation of the peripheral cut end of a posterior nerve root. Lewis considers this dilatation due to the local production of some substance chemically related to histamine. This will be referred to again later.

THE EFFECT OF HORMONES ON CAPILLARIES.—There is ample experimental evidence that extracts of the pituitary gland cause constriction of capillaries (and probably of arterioles as well). Particularly potent are extracts of the pars intermedia called pituitrin. Aldrich has shown recently that this contains at least two different substances, oxytocin (which stimulates the full-time uterus to contract) and vaso-pressin, which has the marked effect on capillaries. (See Chapter XXII.)

Pituitrin, or vaso-pressin, injected under the skin of man produces capillary (and possibly arteriolar) constriction. Further, Milroy's disease, in which oedema of the tissues takes place, is associated with pituitary disease.

There is also experimental evidence that adrenaline constricts capillaries. For if it be injected under the skin there is a local blanching and constriction of capillaries exactly like that produced by pituitrin (vaso-pressin).

THE EFFECT OF HISTAMINE ON CAPILLARIES.—That histamine has a profound dilating effect on capillaries was shown years ago by Dale and his co-workers. Lewis has shown recently that when this substance is injected under the skin (even diluted to 1 in 3000) four effects follow immediately: (a) local dilatation of capillaries; (b) local dilatation of venules; (c) somewhat later dilatation of surrounding arterioles, possibly from some local axon reflex action, or from spread of the histamine to them by diffusion; (d) stagnation of blood in the capillaries and the exudation of fluid into the surrounding tissues, the result being a local swelling or wheal.

These effects of histamine are produced in a number of important circumstances. (1) If the skin be injured, *e.g.* by scratching, freezing, or burning the skin, or applying or injecting numerous chemical substances, *e.g.* cantharides or peptone. (2) If the underlying tissues be injured in any of the above ways. The effect of the histamine may be (a) local, as in a scratch; (b) more generalised, resulting in flushing of the face and other parts of the body; or (c) so generalised that blood pools in all the capillaries and the rest of the circulatory system becomes empty. Such a condition is called secondary surgical shock.

Surgical shock can be stated to be primary when it is caused by a temporary failure in the central nervous system control of the circulatory system. The vaso-motor centre is temporarily paralysed. The arterioles dilate, blood-pressure falls, and cerebral anæmia results. This is the sequence of events when a person faints. Surgical shock can be stated to be secondary when it is caused by the absorption of histamine (or substances chemically

related to it) from extensively lacerated or burnt tissues. The evidence for this statement may be summarised as follows :—

- (a) Histamine can be extracted from most (if not all) organs ;
- (b) It is liberated when tissues are destroyed ;
- (c) If absorbed into the blood-stream, surgical shock develops.
- (d) Surgical shock can be prevented, as Cannon has shown, if the absorption is prevented by clamping the venous return from the damaged limb.
- (e) Poisoning by histamine causes the same symptoms as those of secondary surgical shock. These are : the patient is conscious but makes no voluntary movements ; the limbs are cold, the muscles toneless, and the skin numb (from abolition of skin sensations) ; the heart is rapid but the pulse hardly discernible ; blood-pressure is very low ; cold, thirst, hæmorrhage, bacterial infection, and anæsthetics all tend to make the patient's condition worse. Quite small injuries may induce secondary surgical shock when many are present.

THE EFFECTS OF HEAT ON CAPILLARIES.—If a cold limb is plunged into water at 42° to 45° C. there is at first a sharp pain. This decreases rapidly. At the same time there is marked flushing of the skin. This is due to dilatation of the capillaries, which may be produced by the rise of temperature or to the liberation of histamine in the skin. The arterioles and venules are correspondingly dilated. In consequence of this increased blood-flow the superficial skin structures suffer a fall of temperature from somewhere near that of the water, say 40° to 43° C., to nearly that of the blood, say 38.5° to 39.5° C. It is this fall which causes the initial pain to diminish. A temperature of 45° to 46° C. can now be applied to the limb with very little pain. Experiment shows that the blood leaving such a limb is definitely hotter than that going to it.

If temperatures higher than 46° C. are applied to the skin the typical dilatation of vessels with wheal formation follows. This is later followed by the development of a blister which is caused by the excessive localised liberation of histamine.

THE EFFECT OF COLD ON CAPILLARIES.—The application of cold is similarly followed by effects which vary with the degree of cold applied. If water of 15° to 20° C. is used, the skin becomes blue. This is due to arterial constriction, the capillaries remaining open. The hæmoglobin in the red cells which these capillaries

contain, slowly changes to reduced hæmoglobin from the removal of its oxygen by the surrounding tissues.

If the water applied be 5° to 10° C. the skin becomes red. The arterioles are constricted and the capillaries are toneless and filled with blood. But the red cells do not lose their oxygen since the oxygen utilisation by local structures is stopped. The blood therefore remains red.

Occasionally the skin becomes (or remains) white. This seems to be due to a sudden vaso-constriction (or a continued vaso-constriction) in a limb in which the capillaries and venules were at the time empty. In consequence they contain no red cells and thus the limb does not go either red or blue.

If the skin be frozen, extensive cellular damage follows as in a burn. Much histamine may be liberated.

VARIATIONS IN THE BLOOD DISTRIBUTION IN THE TISSUES.—Since there are three sets of structures present, arterioles, capillaries, and venules, it is clear that from the logical standpoint there are nine possible variations which might be found. So far, however, as is known, the capillaries and venules vary in their dilatation together, which reduces the possible variations to four. These are :

- Arterioles dilated, capillaries and venules dilated ;
- Arterioles dilated, capillaries and venules constricted ;
- Arterioles constricted, capillaries and venules dilated ;
- Arterioles constricted, capillaries and venules constricted.

Observations on various conditions of the skin by means of the microscope show that all four conditions may be met with, and they are found to be accompanied by marked variations in temperature and colour. The skin is warm when the arterioles are dilated whether the capillaries be dilated or not. This presumably means that, even when capillaries are constricted, blood is able to continue passing, but there is no stagnation of blood in the capillary itself, or accumulation of fluid in the surrounding tissues, such as occurs with capillary dilatation. On the other hand, when the arterioles are constricted, the skin is cold, since no blood is able to pass. With regard to colour, the skin is found to be pink when the arterioles are dilated, and the capillaries are just sufficiently dilated to allow quick passage of the blood to take place. It becomes red if the dilatation of the arterioles is accompanied by dilatation of the capillaries ; stagnation in the capillaries is taking place and corpuscles containing oxyhæmoglobin have accumulated in them. The skin becomes white when both arterioles and capillaries are constricted, because no blood is

flowing, and the capillaries are empty. It becomes blue, however, if with arteriole constriction there is capillary dilatation, because no blood is flowing; the capillaries are filled with stationary red blood-corpuscles, the oxygen is removed by the surrounding tissues from the hæmoglobin which these red corpuscles contain. The blue colour of the reduced hæmoglobin causes the skin to be tinted blue.

SECTION III

THE FORMATION OF LYMPH.—Except in the spleen and the liver, the blood does not come into direct contact with the cells of the tissues. It is separated from them not only by the walls of the capillaries, but also by a fluid called lymph, or tissue-fluid, which lies between the capillaries and the tissue-cells themselves. From these spaces the lymph passes into narrow channels (lymphatic vessels) lined by endothelial cells. These channels unite and finally end in a single vessel, the thoracic duct, which opens into the junction of the left jugular and subclavian veins, and conveys the lymph from the greater part of the body into the blood-stream. The lymph from the right side of the head and neck and the right fore-limb, passes into a vessel which opens into the junction of the right jugular and subclavian veins.

Some recent investigations indicate that there is no direct communication between the tissue spaces, filled with tissue fluid, and the lymph capillaries which contain lymph, the lymph capillaries originating, as we know they do, in the villi, as blind tubes in close relation to the tissue fluid.

The lymph was described by Foster as the "middle-man," since, on the one hand, it receives from the blood oxygen and dissolved nutrient materials and passes them on to the tissue-cells, and, on the other hand, it receives from the tissue-cells carbon dioxide and other waste products and returns them to the blood-stream. The interchange of material between the blood and the tissues takes place by diffusion and in this way the tissues are nourished without any change necessarily occurring in the amount of tissue-fluid.

THE COMPOSITION OF LYMPH.—Lymph can be collected by placing a cannula in the thoracic duct of an animal, such as a dog or horse. If the animal has not been recently fed, the lymph is a clear, colourless fluid having a specific gravity of about 1015; it usually clots when allowed to stand. It contains some lymphocytes, 4 to 5 per cent. of protein, the proteins being the same as

those in blood-plasma, and also various salts and extractives. After a meal the lymph is milky in appearance, owing to the presence of large numbers of minute fat-globules. The fat is derived from that taken in the food, which, after absorption from the digestive tract, passes into the intestinal lymphatic vessels (lacteals). In their course the vessels pass through the lymphatic glands, in which lymphocytes are formed; the lymphocytes enter the lymph-stream and are carried into the blood.

EFFECT OF CAPILLARY PRESSURE.—Although the exchange of material between the blood and the tissues does not necessarily increase the amount of lymph in the tissue-spaces, it is found that, in point of fact, lymph is constantly being formed in the body, and, after passing along the lymphatic vessels, is returned to the blood-stream along the thoracic duct. The formation of lymph has been attributed by some writers to secretion by the walls of the capillaries, and by others to the action of purely physical processes such as filtration and osmosis. If the latter view is correct, a rise in capillary pressure should lead to an increase in the formation of lymph; and this is found to be the case.

The flow of lymph is not greatly influenced by alterations in the mean arterial pressure, but is very readily affected by changes in venous pressure; a rise in venous pressure, by obstructing the escape of blood from the capillaries, at once raises the capillary pressure, and this is followed by a great increase in the flow of lymph from the thoracic duct. Hence a large rise in the rate of lymph flow can be produced by ligaturing the inferior vena cava or the portal vein.

HYDRÆMIC PLETHORA.—Again, when a large quantity of saline solution is injected into the circulation, the blood is not only increased in amount, but becomes more watery, the condition being called *hydræmic plethora*. The arterial pressure remains almost unaltered, but the veins are distended to contain the greater part of the fluid added to the circulation, and the venous pressure rises; as a result the pressure in the capillaries also rises, and the flow of lymph is in consequence greatly increased. Much of this enters the lymphatics and the flow from the thoracic duct becomes very profuse.

Hydræmic plethora may be produced by injecting into the blood a strong solution of glucose or other crystalloid body; this raises the osmotic pressure of the blood, and water passes by osmosis from the tissues into the blood, thereby increasing its volume and raising the capillary pressure. In these circumstances

a great increase takes place in the flow of lymph from the thoracic duct, as is seen in the following table :—

HYDRÆMIC PLETHORA

Periods of Ten Minutes.	Arterial Blood-Pressure.	Pressure in Inferior Vena Cava.	Flow of Lymph.
1	100 mm. Hg	12 mm. water	3.0 c.
	40 grm. glucose dissolved in 50 c.c. water injected into a vein.		
2	105 mm. Hg	180 mm. water	33.0 c.c.
3	120 " "	50 " "	31.0 "
4	118 " "	25 " "	20.0 "

From these experiments it may be concluded that the walls of the capillaries form a membrane through which lymph can be filtered off, and that the amount of fluid which passes through the membrane in a given time depends partly upon the capillary pressure.

CAPILLARY PERMEABILITY.—Another factor in the formation of lymph is the variable readiness with which filtration takes place through the capillaries in different parts of the body under the same pressure. The least permeable capillaries are those of the limbs, the most permeable are those of the liver. Under resting conditions almost all the lymph flowing from the thoracic duct is formed in the liver and digestive tract. The permeability of the capillaries can be increased by the injection of various poisonous substances called *lymphagogues*, including peptone and leech-extract. The injection of one or other of these substances into the blood-stream leads to an increased formation of lymph, although the capillary pressure, after a short time, is almost unaltered. The additional lymph is derived almost entirely from the liver, as is shown by the fact that, if the lymphatic vessels of the liver are ligatured, the subsequent injection of peptone does not increase the formation of lymph. Hence these lymphagogues act by damaging the capillaries of the liver, and thus increasing their permeability.

The permeability of the capillaries is also increased when their nutrition is impaired, *e.g.* by lack of oxygen, and such an impairment may give rise to dropsy.

TISSUE METABOLISM.—The formation of lymph is also dependent upon the metabolism of the tissues themselves; increased functional activity of any tissue in the body probably leads to increased formation of lymph. Since the blood-capillaries

are more flushed with blood in an active, than in a resting tissue, and since, as explained on p. 154, many capillaries previously closed become patent during activity, it seems reasonable to regard the accelerated rate of lymph production as due in great part to raised capillary pressure, and to increase in the number and permeability of capillaries in the active tissue. The injection into the blood of bile-salts leads to the secretion of bile by the liver, and the flow of lymph from the thoracic duct is increased. This is only partly due to raised capillary pressure and to changes in the permeability of the capillaries, the rest is due to changed osmotic conditions. In normal circumstances the osmotic pressure of the tissue-cells, the lymph, and the blood is almost the same. When the metabolism of the liver is increased, metabolic products are formed in the liver-cells, raising their osmotic pressure. These products diffuse into the lymph, raising its osmotic pressure, as compared with that of the blood. Consequently, water passes from the blood into the lymph, and this fluid is increased in amount, giving rise to a larger flow from the thoracic duct.

We may conclude, therefore, that lymph-formation is not a secretory process, but is brought about by purely physical processes, namely, filtration and osmosis; and the factors concerned in its production are (1) the capillary pressure, (2) the metabolic activity of the tissues. Under abnormal conditions a third factor, increased permeability of the capillary wall, may become important.

SECTION IV

REABSORPTION OF LYMPH.—If a saline solution containing some readily recognisable substance, such as potassium iodide, is injected under the skin or into the pleural or peritoneal cavity, it rapidly disappears, and the presence of potassium iodide can be demonstrated in the blood or urine some time before it appears in the lymph flowing from the thoracic duct. This experiment makes it clear that water and substances in solution can be readily absorbed from the tissue-spaces through the capillary walls directly into the blood. Similarly, tissue-fluid may be absorbed through the capillary walls. After hæmorrhage, for instance, the volume of the blood is rapidly brought back to the normal by the passage of fluid from the tissue-spaces into the blood. This process depends upon the fact that proteins exert an osmotic pressure, which may be small in comparison with that of a solution of crystalloid bodies, but yet appreciable. The osmotic pressure of the crystalloids in blood and lymph is much the same, but, owing to the percentage of protein in blood being higher than that in

lymph, the blood has a slightly higher osmotic pressure, and fluid tends to pass from the lymph into the blood. At the same time, fluid is being filtered through the capillary wall from the blood into the lymph at a rate varying with the capillary pressure. These two processes, namely, absorption and filtration, tend to balance one another and to keep the volume of the blood constant. The balance may be disturbed either by a rise or by a fall of capillary pressure. In the former case, the amount of tissue-fluid is increased; whereas, if the capillary pressure falls, for instance, after severe hæmorrhage, the amount of fluid absorbed exceeds that which is filtered through the capillary walls, and the volume of the blood is restored at the expense of the lymph and tissues.

THE FLOW OF LYMPH.—Various factors are concerned in bringing about the flow of lymph from the periphery to the thoracic duct. The first of these is the pressure under which lymph passes from the blood-capillaries into the tissue-spaces; this is considerably higher than the pressure in the thoracic duct. Where the duct opens into the great veins the pressure is at most 2 to 3 mm. Hg, and may be negative. Other and more important factors promoting the movement of lymph are muscular and respiratory movements. Every muscular movement, by compressing the lymphatic vessels, forces the lymph on towards the thoracic duct. The contraction of the strands of smooth muscle in the intestinal villi drives the contents of the central lacteal of each villus into the lymphatic vessels. Further, with each inspiration, the abdominal pressure rises and the intestinal lymphatic vessels are compressed; at the same time, the pressure on the thoracic duct becomes negative, and lymph is sucked into it. The effect of these movements is assisted by the presence of valves in the larger lymphatic vessels, which prevent any backward flow of lymph. The flow of lymph from the tissues to the junction of the thoracic duct with the venous system is thus brought about.

THE LYMPH-VESSELS.—The object of these vessels is to drain the lymph away from the tissue spaces. There are two current ideas as to how this is done: (1) That the endothelial cells which line the lymphatic channels form funnel-like connections with the spaces between the tissue-cells. The fluid is thus drained directly into the lymphatic vessel. (2) That a cellular barrier exists between the tissue-spaces and the lymphatic vessels. The following evidence should be considered: In the embryo at all events the tissue-spaces are separated from the lymph channels by a cap of cells which, so far as can be judged

from histological observation, forms a complete barrier between the two, so that materials could only pass from the one space into the other by the physical processes of diffusion and osmosis. When the lymphatic channels are injected the injection mass does not penetrate into the tissue-spaces, which presumably is further evidence of the presence of a barrier. Some histologists believe that the embryonic barriers disappear during development and the reason that injected material does not penetrate into the tissue-spaces is because of the fineness of the constricted lymphatic channels. The lymphatic channels themselves are very like small veins in structure. They have an endothelial lining, round which are circularly and obliquely arranged muscle sheets. These muscle coats are very thin and are not found round the finer lymphatics. The muscles are supplied by non-medullated sympathetic nerve-fibres. The bore of the vessels is presumably, therefore, under the control of the vaso-motor centre, but little or nothing appears to be known of the conditions under which expansion and contraction occur.

In addition to draining the spaces between tissue-cells, the lymphatics also drain intermuscular spaces and serous cavities such as those belonging to joints. In addition, the pleuræ, the pericardium, the abdominal cavity, Tenon's capsule of the eye, the bursæ of tendons, and similar structures are drained by them. They unite, forming larger vessels which usually pass through lymphatic glands on their course.

LYMPHATIC GLANDS.—These are small kidney-shaped structures having an outside fibrous capsule. Fibrous bands run in from this, dividing the gland into a number of compartments. Accompanying these compartments are endothelium-lined lymph spaces. The lymph flowing to the gland enters these spaces by a number of connecting vessels and having flowed through these spaces gains access to the interior of the compartments. An artery accompanied by its vein enters the gland at its hilus; a branch travels towards the centre of each of the compartments and breaks up into a number of capillaries. Crowded masses of dividing lymphocytes are collected round these capillaries and fill the interior of the compartments, which also contain reticulo-endothelial cells. The lymph percolates through the superficial parts of these masses so that the newly formed lymphocytes enter the stream. This now collects at the hilus, where a lymphatic vessel once more conveys the lymph on and, joining other lymphatic vessels, ultimately reaches the thoracic duct and so enters the blood-stream. It is in this way that the supply of lymphocytes to the blood is maintained, the number in normal

blood being about 2,000 per cubic millimetre, *i.e.* they form about 25 per cent. of the white cell content of the blood. Bacteria that have gained access to the tissues tend to pass along lymphatic channels and, reaching the lymphatic gland, are usually destroyed by the reticulo-endothelial cells there. In bad health, on the other hand, the bacteria may get the upper hand, the result being tenderness and swelling of the glands and of the structures surrounding them. This condition may necessitate surgical interference.

LYMPHOID TISSUE.—Tissue similar to that forming the lymphatic glands is found in the hæmal lymph glands of certain animals. These differ from lymphatic glands in being red in colour. In the tonsil the lymphoid masses are covered by stratified epithelium which is interrupted by crypts. Smaller masses of lymphoid tissue are found at the back of the tongue and in various other places in the nasal pharynx (adenoids). They are also found in other situations, namely, in the solitary glands and Peyer's patches of the intestinal tract. Lymphoid tissue is also found in the spleen and in the thymus gland. These structures are described in detail elsewhere.

CHAPTER VIII

THE RESPIRATORY SYSTEM

SECTION I

THE STRUCTURE OF THE AIR-PASSAGES AND LUNGS.—

Respiration consists in the transference of oxygen from the atmospheric air to the tissues of the body, and of carbon dioxide from the tissues to the outer air. In man and most vertebrates, the oxygen and carbon dioxide are carried to and from the tissues respectively by the blood, which, on the one hand, receives oxygen in the lungs and gives it up to the tissues, and, on the other hand, receives carbon dioxide from the tissues and gives it up in the lungs. In fishes and many invertebrates, the lungs are replaced by gills. The transference of oxygen from the atmosphere into the blood, and of carbon dioxide from the blood into the atmosphere, is called *external* respiration, the interchange of gases between the blood and the tissues being termed *internal* or *tissue* respiration. The respiratory system consists of the lungs and the air-passages leading to them, namely, the mouth and lower half of the nasal cavity, the upper part of the pharynx, the larynx, trachea, and bronchi.

THE TRACHEA.—This is a wide tube about $4\frac{1}{2}$ inches in length in man, which is lined by stratified epithelium, the cells of the inner layer being columnar and ciliated. The epithelium rests upon a thick basement-membrane, beneath which is a layer of elastic fibres running longitudinally; external to this is areolar tissue in which lie many small glands which secrete mucin; outside this is a fibrous coat, strengthened by C-shaped hoops of cartilage. The posterior wall of the trachea contains a layer of unstriped muscle, most of the fibres of which run transversely between the free ends of the cartilages. The cartilaginous hoops keep the lumen of the trachea patent, and prevent its occlusion by external pressure. The fluid formed by the small mucous glands moistens the inner surface of the trachea and serves also to catch bacteria or particles of dust which may be carried in

with the inspired air ; the cilia, by their movement, carry both the fluid and the foreign bodies up the trachea towards the pharynx.

THE BRONCHI are similar in structure to the trachea.

In the lungs the bronchi branch in a tree-like manner, the final ramifications opening into the pulmonary air-cells. The *larger intra-pulmonary bronchi* are lined by a ciliated columnar epithelium resting on a basement-membrane. Lying under the basement-membrane are longitudinally disposed elastic fibres with loose connective tissue. More externally is a layer of circularly arranged smooth muscle-fibres, the *bronchial muscle*. External to the bronchial muscle is a fibrous coat containing scattered, irregular plates of hyaline cartilage. The *smaller bronchi* (bronchioles) have no cartilaginous plates, but their muscular coat is well marked.

THE ALVEOLI.—Each bronchiole leads into a small number (three or four) of wider thin-walled spaces, lined by flattened epithelium, called *atria* (Fig. 73). Out of each atrium open two or three blind diverticula, each of which is called an *infundibulum*. The walls of the infundibula are studded with hemispherical sacs known as *alveoli*, which are lined by flattened, non-nucleated, epithelial cells. Between adjacent alveoli there is a dense network of capillaries, supported by a small amount of fine connective and elastic tissue ; the network of capillaries is thus common to the two adjacent alveoli, and the blood in the capillaries is separated from the air in the alveoli merely by two thin layers of epithelium. In birds, even the alveolar epithelium appears to be absent, the blood and air being separated solely by the capillary wall.

The branches of the pulmonary artery accompany the bronchi, and open into the alveolar capillary network, from which blood is carried back to the left auricle by the pulmonary veins. Oxygenated blood is supplied to the bronchi by the bronchial arteries.

THE PLEURÆ.—The lungs nearly fill the thoracic cavity, the space between them being occupied by the heart, great vessels, and other structures. Each lung is covered by a thin membrane, consisting of a superficial layer of flattened epithelium resting on connective tissue with many elastic fibres ; the membrane is known as the *pleura*, and is reflected at the root of the lung on to the chest-wall. Each pleura forms a closed sac, the walls of which are normally in apposition ; their inner surfaces are

moistened by a small amount of fluid, resembling lymph, and glide over one another with every movement of the chest-wall and lung. The thorax is a completely closed box, which alters in shape and size with each respiratory movement; with inspiration it

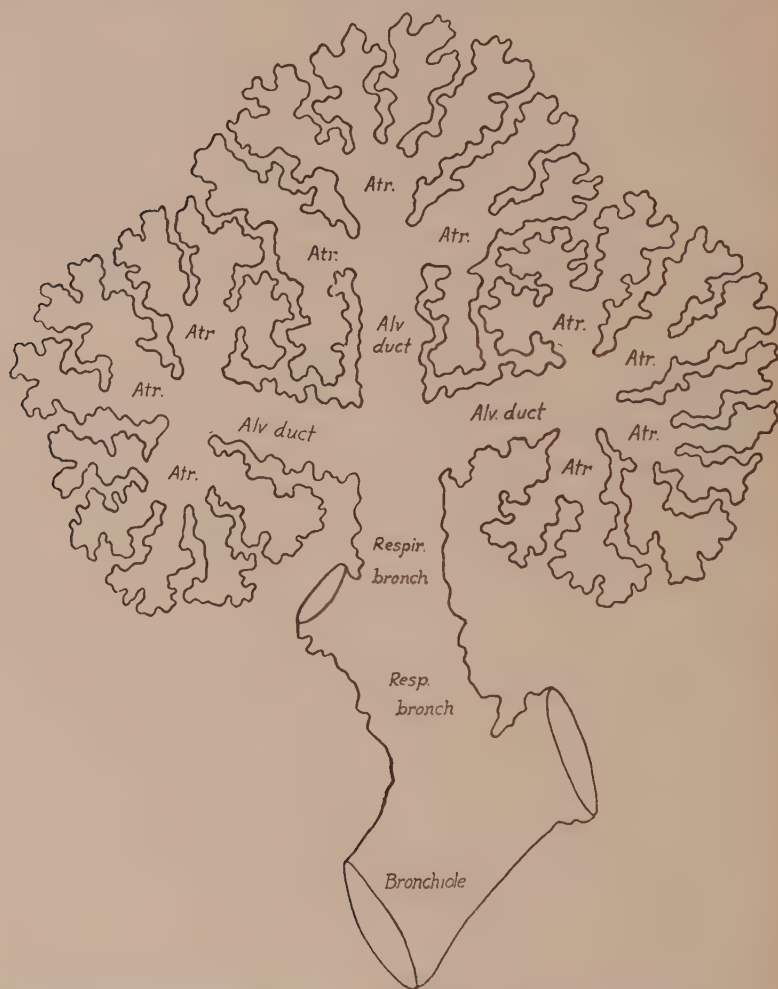


FIG. 73.—Diagram of three lung lobules, showing the mode of termination of a bronchiole. (From Haldane's *Respiration*, after Miller.)

becomes larger in all its dimensions, vertical, antero-posterior, and transverse, returning to its former size during expiration. The increase in size is brought about partly by the upward movement of the ribs, partly by the descent of the diaphragm.

THE DIAPHRAGM consists of a muscular sheet with a tendinous central portion. In the position of rest it forms a dome projecting towards the thoracic cavity, and when it contracts the summit of the dome—namely, the tendinous portion—is drawn downwards from 1 to 2 cm., thereby increasing the vertical dimensions of the chest. The extent to which the central tendon can be drawn downwards is limited by the resistance of the abdominal viscera, and, when the limit is reached, the direction of the pull of the costo-sternal muscle-fibres of the diaphragm is reversed, so that the lower end of the sternum and the movable ribs are raised. The spinal fibres of the diaphragm, the lower attachment of which is a fixed point, exert a downward pull upon the central tendon throughout the inspiratory period.

THE CHEST.—During inspiration the first pair of ribs and the manubrium sterni are fixed by the resistance of the cervical structures, and the second to the fifth pairs of ribs are drawn upwards by the contraction of the external intercostal muscles and the serratus posticus (posterior) superior. Since the ribs slant downwards and forwards from their vertebral articulation, this upward movement carries the sternum forward and increases the antero-posterior dimensions of the chest. At the same time the ribs rotate slightly round the axis represented by a line drawn from their vertebral to their sternal attachments, and their lower borders, which in the expiratory position are inverted, become everted. The costo-chondral angle is also opened out. By these means the transverse dimensions of the chest are enlarged.

The lower ribs are raised partly by the external intercostal muscles, partly also by the contraction of the diaphragm, and partly by the interchondral portion of the internal intercostal muscles.

SECTION II

THE RESPIRATORY MOVEMENTS.—The muscles concerned in quiet inspiration are the diaphragm, the external intercostal muscles, the interchondral portion of the internal intercostal muscles, and the serratus posticus (posterior) superior. The entrance of air into the lungs is also assisted by widening of the glottis, and, if the breathing is at all laboured, by dilatation of the alæ nasi. In forced inspiration other muscles, such as the trapezius, pectoral, sternomastoid, and rhomboid, are called into play.

During quiet expiration, the chest returns to its former shape and size, mainly on account of the elasticity of the chest-wall and

lungs and of the abdominal wall and abdominal contents; the downward movement of the ribs during expiration is also assisted by the contraction of the costal part of the internal intercostal muscles. In forced expiration, the accessory muscles employed are mainly those of the abdominal wall.

Quiet respiration is carried out principally by the movements of the diaphragm. When lying down movements of the diaphragm are impeded by the abdominal viscera and respiration in consequence becomes more costal in type, *i.e.* it is carried out by chest rather than by diaphragmatic movements.

A MODEL OF THE CHEST AND LUNGS.—The conditions which bring about the passage of air into, and out of, the lungs during respiration can be roughly illustrated by the aid of an artificial model. A thin-walled rubber bag is placed in a glass vessel closed by a cork; the bag is attached to a glass tube, which passes through the cork and is open at the top. The bottle is connected by another tube with a mercury manometer, and by a third tube with a suction-pump, by means of which air can be sucked out of it (Fig. 74).

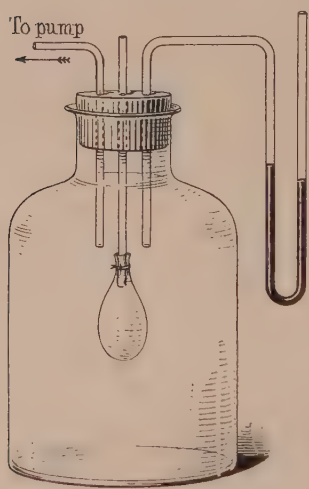


FIG. 74.—For explanation see text.

At the outset of the experiment the air in the bottle is at the same pressure as that of the atmosphere, and the bag is collapsed. If a little air is sucked out of the bottle, the pressure falls and, since the pressure within the rubber bag remains unaltered, a difference of pressure is set up on its inner and outer surfaces. The bag therefore expands, air being sucked into it along the glass tube to fill the extra space thus provided, until the pressure within it and outside it becomes nearly equal; but the pressure outside the bag is finally a little less than atmospheric pressure, because a part of the pressure on the inner surface of the bag is used up in overcoming the tendency of its stretched elastic wall to collapse.

When more air is sucked out of the bottle, the rubber bag expands still further, but the pressure in the bottle remains negative, that is, less than atmospheric pressure. When the bottle is opened, the bag collapses because the pressure on each side of it becomes the same.

VARIATIONS IN NEGATIVE PRESSURE.—In the body the lungs take the place of the bag, the bottle is represented by the chest, and the changes in the pressure on the outer surface of the lungs are brought about by alteration in the size of the chest-cavity. If a small tube, connected with a manometer, is passed through the chest-wall of an animal into the pleural cavity, the pressure within the chest is seen to be lower than that of the atmosphere; at the end of expiration the difference is usually about 6 mm. Hg. When the chest enlarges during inspiration, the pressure on the outer surface of the lungs diminishes, and, as the pressure within them remains unchanged, they expand. Owing to the greater force required to bring about this expansion of the lungs, the pressure in the pleural cavity is further diminished, and amounts on an average to 30 mm. Hg. The negative pressure in the pleural cavity thus varies from -6 mm. Hg during expiration to -30 mm. Hg or more during inspiration, and represents the suction required to overcome the tendency of the expanded lungs to collapse by virtue of their elasticity. When the lungs expand during inspiration, air rushes in to fill the additional space; during expiration air is expelled. The expansion of the lungs during inspiration is due almost entirely to the enlargement of the infundibula and atria, and the portions of the lungs which expand most are those in contact with the diaphragm and ribs; the dorsal and mediastinal surfaces, and the apices usually expand less.

COLLAPSE OF THE LUNGS.—If the chest is opened, either during life or after death, the pressure on both the outer and the inner surfaces of the lungs is that of the atmosphere, and owing to their elasticity the lungs collapse. In the new-born infant, the lungs, even in their collapsed condition, fill the chest. As the child grows, the capacity of the chest increases more rapidly than does the size of the lungs; and the lungs of the adult are considerably expanded even at the end of expiration.

TIDAL AIR.—Since with each expansion of the chest the lungs increase in size so as completely to fill the extra space thus provided, the amount of air entering the lungs at each breath varies with the extent of the respiratory movement. In quiet respiration it amounts to 350 to 500 c.c., and is spoken of as *tidal* air. The additional volume of air which can be taken into the lungs by forced inspiration amounts on an average to about 2000 c.c., and is called *complemental* air. The largest amount of air which can be expelled from the lungs by the most violent expiration, made

at the end of an ordinary breath, is termed *supplemental* air; it varies in different individuals, but is about 1500 c.c.

VITAL CAPACITY.—The total volume of air which can be taken into and expelled from the lungs by the most forcible inspiration and expiration, namely, the sum of the tidal, complementary, and supplemental air, is termed the *vital capacity* of the chest, and is about 4000 c.c. These figures are obtained by allowing the individual to breathe through a gas-meter, or else into a spirometer, which is a small graduated gasometer.

RESIDUAL AIR.—Even after the most forcible expiration a considerable amount of air—usually at least 1000 c.c.—still remains in the lungs, and is spoken of as *residual* air (Fig. 75).

Complemental air = 2,000 c.c.	} Vital capacity = 4000 c.c.
Tidal air = 500 c.c.	
Supplemental air = 1,500 c.c.	
Residual air = 1,000 c.c.	

FIG. 75.

The volume of residual air can be found as follows:—the subject makes a forced expiration, as complete as possible; he then *rapidly* takes two or three *deep* breaths in and out of a bag containing a known volume of pure hydrogen, finally ending with a complete forced expiration into the bag; the contents of the bag are then analysed. Suppose the bag, to begin with, held 5 litres of hydrogen, while at the end it contained 4 litres of hydrogen diluted with 1 litre of residual air. The other litre of hydrogen must now

be in the lungs, and since the hydrogen and the residual air have been uniformly mixed in bag and lungs, this hydrogen must also be diluted with $\frac{1}{4}$ of its volume, or 250 c.c., of residual air. The total volume of residual air is therefore 1·25 litres.

THE RATE OF RESPIRATION.—The normal rate of respiration in adults is 15 to 18 a minute. Expiration follows inspiration immediately, and is succeeded by a slight pause before the next inspiration begins. Children breathe more rapidly, the rate in the infant being about 40 a minute.

Ordinary quiet breathing is usually called *eupnœa*, and an increase in the depth of the respiratory movements is called *hyperpnœa*; if these movements are not only deeper, but also laboured, the term *dyspnœa* is applied to them. A temporary cessation of breathing is known as *apnœa*.

THE BREATH-SOUNDS.—If the sounds produced in the trachea owing to the to-and-fro movement of the air be listened to with a stethoscope, a sharply defined rustling sound is heard during both inspiration and expiration. Its intensity appears to depend on the velocity of the current of air. If, on the other hand, we listen to the sounds occurring in normal lung by applying the stethoscope to one of the intercostal spaces, a sound is heard during inspiration only, which is very likely due to eddies set up in the alveoli owing to the jet of air which enters from the bronchioles. The lung-sound is called a vesicular murmur. It is not heard at any part of the chest where air is not entering the underlying lung. Nor is it heard if the two layers of pleuræ are separated, *e.g.* by effused fluid.

The to-and-fro sound which occurs in the air passages is called a bronchial murmur. It is not as a rule heard on listening at different parts of the chest unless the intervening lung is solid, *e.g.* during pneumonia.

METHODS OF RECORDING RESPIRATORY MOVEMENTS.—

In order to obtain graphic records of the rate and depth of the respiratory movements the following methods have been devised.

(1) In man the respiratory movements can be recorded by a *stethograph*, one form of which consists of a small metal cylinder provided with a lateral opening and closed at each end by a rubber membrane; the lateral opening is connected by rubber tubing with a tambour. Strings are attached to the centre of each rubber membrane, and are passed round the chest and tied. Each expansion of the chest causes the strings to pull upon the rubber membrane, so that the capacity of the cylinder increases and the lever of the tambour falls: during expiration the membranes return to their former position. The same apparatus can be used to record the respiratory movements in the lower animals.

(2) Another method, used in animals, is to connect the side piece of a cannula, inserted into the trachea, with a tambour; with each inspiration air is sucked out of the tambour, and the lever falls.

(3) In rabbits, a small slip of the diaphragm on each side is inserted into the xiphisternum: this strip of muscle can be isolated without interfering with its vascular or nervous connections. It contracts synchronously with the rest of the diaphragm, and serves as an index of the movements of the diaphragm as a whole (Head's method).

SECTION III

THE CHEMISTRY OF RESPIRATION.—The composition of expired air differs considerably from that of the atmosphere, the average difference being as follows :—

	Nitrogen.	Oxygen.	Carbon Dioxide.
Inspired air . . .	79	20.96	0.04
Expired air . . .	79.4	16.50	4.10
		4.46	4.06

The increased percentage of carbon dioxide in expired, as compared with inspired, air is 4.06, the difference between the percentage of oxygen in inspired and expired air being 4.46, so that the total volume of the air expired is less than that inspired. It is for this reason that the *relative* amount of nitrogen in expired air is slightly increased, although the total amount expired is the same as that inspired. In the above table, therefore, every 100 c.c. of expired air is derived from $\frac{79.4 \times 100}{79}$ c.c.

of inspired air which contains $\frac{79.4 \times 20.96}{79} = 21.07$ c.c. of oxygen; the oxygen which has disappeared *per 100 c.c. of expired air* is therefore not 4.46 c.c., but $21.07 - 16.5 = 4.57$ c.c.

THE RESPIRATORY QUOTIENT.—The ratio of the *volume* of carbon dioxide leaving the body to the *volume* of oxygen absorbed in the lungs during the same time is known as the *respiratory quotient*, and is expressed as $\frac{\text{CO}_2}{\text{O}_2}$. In the above example it is $\frac{4.06}{4.57} = 0.89$. Its significance will be discussed subsequently in Chapter XVII.

In addition to containing less oxygen and more carbon dioxide, the expired air is saturated with water, and is near the body temperature. The symptoms of discomfort experienced in ill-ventilated rooms are due partly to the accumulation of carbon dioxide in the air, and partly, as Leonard Hill suggests, to high temperature, to moisture, and to lack of currents of air in the room. (See Chapter XIX.)

The earlier part of the expired air comes from the respiratory passages, namely, the bronchi, trachea, pharynx, and nose. The latter part comes from the alveoli. The former is known as the "dead space" air. Its volume is about 140 c.c. Since the interchange of oxygen and carbon dioxide between the blood and the air in the lungs takes place solely in the alveoli, it is of great importance to ascertain the composition of the alveolar air.

ALVEOLAR AIR.—Haldane has devised a simple apparatus for collecting samples of *alveolar air* in man. It consists of a piece of rubber tubing about 1 inch in diameter, 3 or 4 feet long, and provided with a mouthpiece. About 2 inches from the mouth-piece the tube is connected with a sampling tube (Fig. 76) which has previously been made vacuous. The subject breathes normally for a few moments, and then, at the end of a normal inspiration, he expires deeply through the mouth-

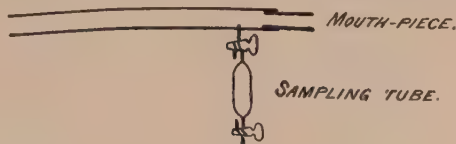


FIG. 76.

Haldane's alveolar air sampler.

piece and instantly closes the mouthpiece with his tongue. The part of the tube near the mouthpiece is now full of alveolar air. The upper tap of the sampling tube is at once opened, and alveolar air rushes into it from the tube; the tap is then closed, and the sample can be analysed.

The amount of carbon dioxide in alveolar air obtained by this method varies from 5 to 6 per cent. in different individuals, but is remarkably constant in the same individual at constant barometric pressure; the amount of oxygen is usually 13 to 14 per cent. Alveolar air thus contains considerably less oxygen and more carbon dioxide than ordinary expired air, the reason being that, in the expired air, the alveolar air is mixed with the contents of the dead space, the composition of which differs but little from that of the atmosphere.

AIR ANALYSIS.—The air is analysed by exposing a known volume of it to caustic potash, which absorbs the carbon dioxide; the diminution in volume represents the amount of carbon dioxide present in the air. The air is then treated with pyrogallate, which absorbs oxygen, and the diminution in volume is again measured. The residual gas is nitrogen.

THE GASES IN THE BLOOD.—Before discussing the means by which the interchange of oxygen and carbon dioxide between the

blood and air in the lungs is effected, it is necessary to determine, first, the amount of these gases in the blood, and, second, the conditions in which they are held in it.

Samples of human blood are easily obtained for analysis; arterial blood is drawn by a glass syringe provided with a fine hypodermic needle which is pushed into the radial artery, this procedure being known as *arterial puncture*; samples of venous blood can be drawn in a similar manner from any convenient superficial vein; to prevent clotting about 0·5 per cent. of powdered potassium oxalate is added to the blood in the syringe.

If blood is exposed to a vacuum, there is a considerable evolution of gas, which may be collected and analysed. For this purpose a special vacuum gas-pump used to be employed. This method necessitates the use of comparatively large quantities of blood (10 to 20 c.c.) in order to give accurate results.

BLOOD-GAS ANALYSIS.—We now have apparatus by means of which the estimation of the blood-gases can be carried out with very small quantities (1 c.c. or even 0·1 c.c.) of blood. The method has the advantage of being readily applicable to man, and depends upon the fact that, when potassium ferricyanide and a trace of alkali (usually ammonia) are added to blood, all the oxygen previously in combination with hæmoglobin is evolved, and the amount of oxygen given from a known volume of blood can be measured. The hæmoglobin then takes up oxygen from the reagents, and is converted into methæmoglobin.

On subsequent treatment of the sample of blood with an acid, all the carbon dioxide present in the blood is given off and its amount can be measured. Recent observations indicate that the following figures represent approximately the amount of oxygen and carbon dioxide present in 100 volumes of human blood :—

	Oxygen.	Carbon Dioxide.
Arterial blood	18-18·5 vols.	45 vols.
Venous blood	12-14 „	50-51 „

One apparatus that may be used is shown in Fig. 77.

There are also from 1 to 2 volumes per cent. of nitrogen in the blood, held in physical solution.

The above figures for venous blood refer to mixed blood in the great veins. The composition of blood from superficial veins is very variable.

OXYGEN CAPACITY.—The maximum volume of oxygen which 100 volumes of blood can contain, when fully saturated, is called its *oxygen capacity*. It is usually about 19 volumes per 100 volumes of blood. If, then, blood contains about 14 per cent. hæmoglobin, each gramme of hæmoglobin combines with

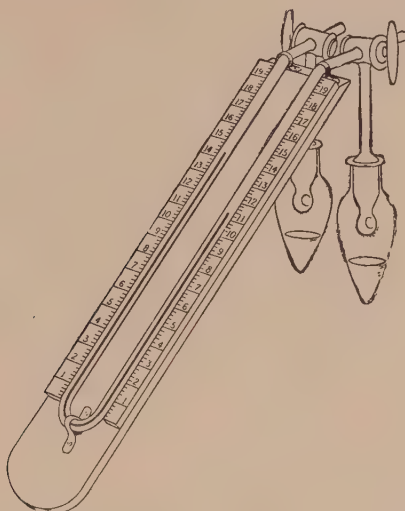


FIG. 77.—Barcroft's blood-gas apparatus. (From Barcroft's *Respiratory Function of the Blood*.)

1.34 c.c. oxygen. If we take 19 volumes as the oxygen capacity of blood, arterial blood, which contains 18 to 18.5 volumes, is not quite fully saturated, but contains only about 95 to 98 per cent. of the full amount. This is due to the time taken by the blood to pass through the lungs being not quite sufficient for complete oxygenation.

THE CONDITION OF GASES IN BLOOD.—Theoretically, gases might be either simply dissolved in the blood, or chemically combined with one of its constituents. In order to decide which of these possibilities is the correct one, it is necessary to consider first the conditions which modify the amount of any gas dissolved in a fluid such as water. On exposing water to the air, a certain amount of oxygen and nitrogen dissolves in it. Confining our attention to the oxygen, the amount dissolved in a known volume of water depends upon (1) the capacity of water to dissolve oxygen, (2) the pressure exerted by the oxygen upon the surface of the water, and (3) the temperature of the water. The solubility in

water of a gas is constant, provided the pressure of the gas and the temperature of the water remain unchanged. Some gases, such as carbon dioxide, are very soluble in water; others, such as oxygen and nitrogen, much less so. The *coefficient of solubility* of a gas is defined as the amount of that gas which is dissolved at a given temperature in 1 c.c. of the liquid, when the pressure of the gas in the liquid is 760 mm. Hg.

Since the solubility of any gas is constant, the amount of the gas dissolved at a given temperature varies directly with the pressure of the gas on the surface of the liquid. If water is exposed to pure oxygen at atmospheric pressure, the pressure of oxygen in the water is 760 mm. Hg. If water is exposed to atmospheric air, both the oxygen and nitrogen exert this pressure, which is divided between them in proportion to their percentage in the air. The oxygen contributes therefore $\cdot 2096 \times 760$ ($= 159$ mm. Hg), and the nitrogen $\cdot 7904 \times 760$ ($= 601$ mm. Hg). These 159 and 601 are known as the partial pressures of these gases respectively. The percentages and partial pressures of oxygen and CO_2 in alveolar air are :

	O_2	CO_2
Per cent. in alveolar air . . .	14	5.5
Partial pressure in alveolar air . .	105	42

THE TENSION OF GAS IN A FLUID.—When water is exposed to a gaseous mixture containing oxygen, the molecules of oxygen tend to pass into the liquid and be dissolved; at the same time, the molecules of oxygen already in solution tend to pass from the water into the gaseous mixture. The tendency of the molecules of oxygen to leave the fluid is called the *tension* of oxygen in the fluid. When these two opposing processes are equal, the gaseous mixture and the fluid are in equilibrium, and the amount of oxygen dissolved in the fluid remains constant. In these circumstances the tension of oxygen in the fluid is equal to the partial pressure of the oxygen in the gaseous mixture to which the fluid is exposed.

The tension of oxygen or other gas in a fluid cannot be measured directly, but can be determined by finding what mixture of gases remains unaltered in composition when exposed to the fluid, *i.e.* by finding a gas mixture which is in equilibrium with the fluid. This gas can then be analysed by potash and pyrogallol, and the tension ascertained by calculation. For example, if the amount of oxygen in a gaseous mixture is 5 per cent. and the total pressure of the gaseous mixture is 760 mm. Hg, the partial pressure of oxygen in the gas is 38 mm. Hg, and this is equal to the tension

of oxygen in the fluid. The apparatus for measuring the tension of a gas in a fluid is called an *aerotonometer*.

THE AEROTONOMETER.—Krogh has devised an aerotonometer which can be used to measure the tension of oxygen in circulating arterial blood, and the lower part of it is shown in Fig. 78. It consists of a cannula A, which is attached to the central end of an artery; the blood flows from the cannula into a bulb B, from the top of which passes off a narrow graduated tube. A small air-bubble C is placed in the bulb, and the blood flows through the bulb, and is returned to the distal end of the artery by the tube D, clotting being prevented by the injection of hirudin. An interchange of gases takes place between the blood and the bubble, and, owing to the small size and relatively large surface of the latter, the gases in the blood and the bubble soon come into equilibrium, this being reached when the size of the bubble remains constant; it is then withdrawn into the graduated tube and its composition is analysed.

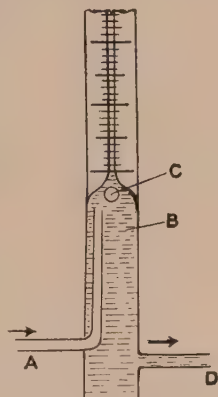


FIG. 78.—Krogh's aerotonometer.

Since the oxygen of the blood is in equilibrium with that in the bubble, the tension of oxygen in the blood can be ascertained by determining the percentage of oxygen in the bubble and the total pressure to which it is exposed. If the arterial pressure is 100 mm. Hg, the total pressure to which the bubble is exposed is atmospheric pressure (say 760 mm. Hg) + arterial pressure (say 100 mm. Hg); total, 860 mm. Hg. If, then, analysis shows that the bubble contains 10 per cent. of oxygen, the partial pressure of oxygen is 10 per cent. of 860 mm. Hg (atmospheric + arterial pressure), namely, 86 mm. Hg. The tension of oxygen in this blood is thus equal to 86 mm. Hg, or about 11.3 per cent. of an atmosphere.

PASSAGE OF OXYGEN THROUGH THE LUNGS.—If oxygen is at all like other chemical substances, and if the lung is at all like other glands, there are two ways in which oxygen could pass from the air in the alveoli into the corpuscles in the blood: by diffusion and by secretion. The former depends on suitable physical conditions and a larger partial pressure of oxygen in the alveoli than in the blood. The latter depends on suitable physiological conditions and the right kind of secreting cells in the lung alveoli. Most physiologists are agreed that the conditions for diffusion are

present, while those for secretion are not. Let us examine the figures.

Partial pressure of O_2 in alveolar air .	105 mm. Hg
Tension of O_2 in venous blood . . .	35 mm. Hg
„ „ arterial blood . . .	95 mm. Hg .

Since the tension of O_2 in venous blood is 35 mm. Hg, the partial pressure there is about 70 mm. Hg below that in the alveoli. At first this difference of pressure is available to cause diffusion of O_2 from the alveoli into the lungs. But as the blood acquires O_2 and becomes arterial this pressure difference is reduced to only 10 mm. Hg. These differences of pressure have to cause the O_2 to pass through the thin lining cells of the alveoli; then across a very narrow tissue space filled with fluid; then through the very thin capillary wall; then through the cell wall of the red blood-corpuscles; and, lastly, the hæmoglobin has to combine with the oxygen. All these processes have to occur in the time during which the corpuscles flow through the lung capillaries. Calculations by Roughton and others show that the time and pressure available are sufficient even in the more rapid flow and increased oxygen requirement of active exercise if the oxygenation of the hæmoglobin does not cause delay.

RAPIDITY OF COMBINATION OF BLOOD WITH OXYGEN.—

Experiment shows that this combination is an extremely rapid one. The apparatus (see Fig. 79) caused reduced blood to be mixed with oxygenated Ringer's fluid and then caused it to flow in a steady stream through a glass observation tube. The reaction which occurred in this could be measured by changes which took place in the absorption bands by means of the reversion spectroscope. These changed from those of reduced hæmoglobin to those of oxyhæmoglobin. The change took less than one-hundredth part of a second.

Similar determinations on red blood-corpuscles by Hartridge and Roughton showed that they became saturated with oxygen in about one-twentieth part of a second; so rapidly, in fact, as to have normally no appreciable limiting effect on the rate of oxygen uptake by the blood in the lungs.

HOW BLOOD CARRIES OXYGEN.—In the first place we know that 100 c.c. blood can hold, when fully saturated, 19 c.c. of oxygen. Experiment shows that less than 0.4 c.c. is in physical solution; that is, that 18.6 c.c. is chemically combined with hæmoglobin. We have seen in the last section that this process is

very swift. We must now consider how this combination takes place in the blood and how the equally important dissociation of that oxygen from the blood occurs at the tissues. Suppose we place 100 c.c. of blood into each of six litre bottles. The first bottle, which contains air at atmospheric pressure, has a partial pressure of oxygen in it of about 160 mm. Hg. The blood is shaken with the air for fifteen minutes in a water-bath at the normal human

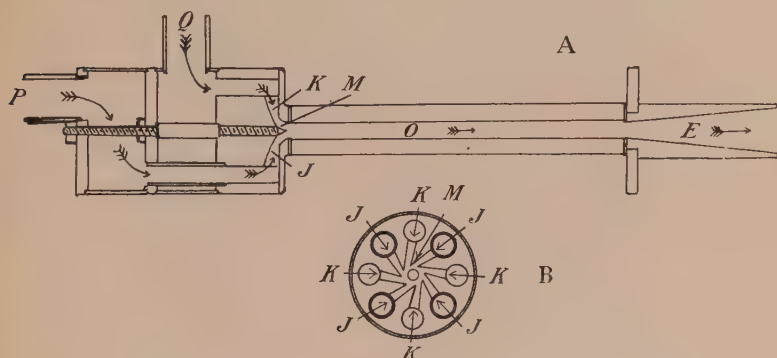


FIG. 79.—Mixing apparatus. (Hartridge and Roughton.)

A, Longitudinal section of the apparatus. *P*, entry for *e.g.* reduced blood; *Q*, entry for *e.g.* oxygenated Ringer's fluid; *J*, one of the four jets for *e.g.* reduced blood; *K*, one of the four jets for *e.g.* oxygenated Ringer's fluid; *M*, mixing chamber for the two fluids; *O*, observation tube in which the reaction takes place; *E*, venturi tube exit. The fluids are usually driven into the apparatus at a pressure of 10 pounds per square inch.

B, Plan of the jets and mixing chamber. *J*, *J*, *J*, and *J* indicate the four jets for *e.g.* reduced blood; *K*, *K*, *K*, and *K* indicate the four jets for *e.g.* oxygenated Ringer's fluid. They enter the mixing chamber *M* tangentially as shown, thus setting up a rotary motion in the liquids and very rapid mixing.

temperature of 37° C. The blood is now analysed and is found to have 18 c.c. of oxygen in chemical combination. This is nearly the maximum possible. The blood is almost "saturated." The second bottle is similarly treated, but the partial pressure of oxygen is reduced to half that in the first bottle, namely, to 80 mm. Hg. Subsequent analysis shows 17 c.c. of oxygen in combination, or 95 per cent. of the saturation value. The blood from bottle 3, which had an oxygen partial pressure of 40 mm. Hg, is found to have 12 c.c. of oxygen; that is, the blood is roughly 67 per cent. saturated. Similarly, at 20 mm. partial pressure the blood still contains 28 per cent. of the maximum amount possible; while at 10 mm. pressure it is still about 6 per cent. These results are shown in Fig. 80. The graph is called a dissociation-curve. Now we know the partial pressure of oxygen in arterial blood to be 95 mm. Hg, while in venous blood it is 35 mm. Hg. Referring to Fig. 80, we see that blood is about 95 per cent. saturated at 95 mm. Hg, and about 60 per cent.

saturated at 35 mm. Hg. On arterial blood becoming venous the saturation of the blood would change from 95 to 60 per cent., *i.e.* by 35 per cent. of the amount which it holds when saturated. Now 100 c.c. of blood holds, as we have said, about 19 c.c. of oxygen when saturated; 35 per cent. of 19 c.c. is 6.6 c.c. But the tissues of an ordinary resting man require

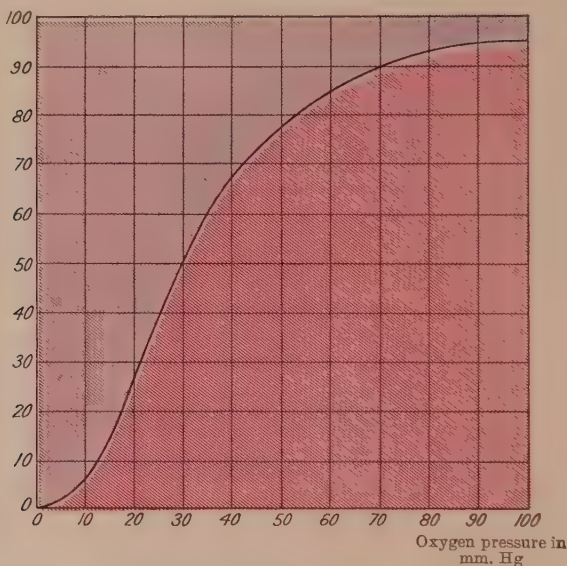


FIG. 80.—Dissociation-curve of blood at 37° C.
(From Barcroft's *Respiratory Function of the Blood.*)

Blood is red, and reduced blood is purple.

roughly 330 c.c. of oxygen per minute. Since 100 c.c. of blood provides 6.6 c.c., then 5000 c.c. will have to circulate per minute to provide 330 c.c. If then his heart beats 70 times per minute it will have to pump at each stroke about 70 c.c. Now we know that in resting man about 7000 c.c. circulate per minute and that the heart at each stroke pumps 100 c.c. There is, therefore, at rest, rather more blood circulating than is actually necessary to provide the tissues with the oxygen they require. When performing work, on the other hand, the circulation rate would have to be increased. The way this increase is effected will be discussed in Chapter IX.

THE UPTAKE OF OXYGEN BY THE BLOOD.—The form of the dissociation-curve for blood can be greatly altered by varying circumstances, and it differs considerably from that of a

solution of pure hæmoglobin, as may be seen in Fig. 81. A comparison of the two curves shows that oxyhæmoglobin dissociates more readily in blood than when simply dissolved in water. When the partial pressure of oxygen is 20 mm. Hg, blood contains only 30 per cent. of its hæmoglobin in the form oxyhæmoglobin, whereas in an aqueous solution of pure hæmoglobin 72 per cent.

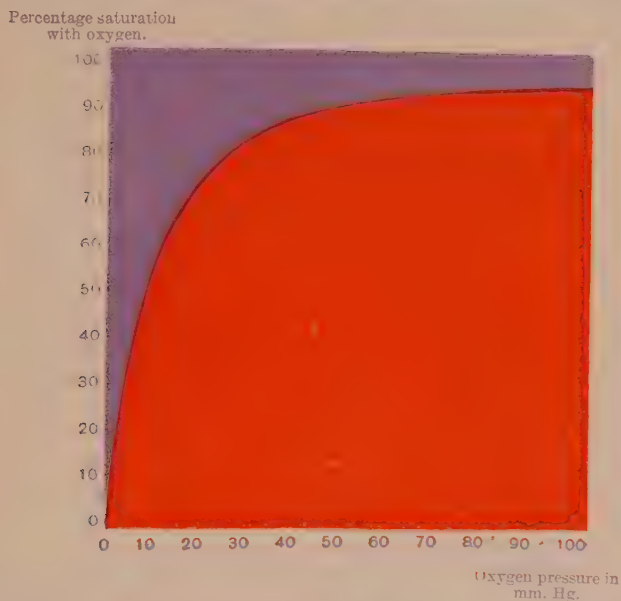


FIG. 81.—Dissociation-curve of hæmoglobin dissolved in water at 37° C.
(From Barcroft's *Respiratory Function of the Blood*.)

Oxyhæmoglobin is red, and reduced hæmoglobin is purple.

exists as oxyhæmoglobin. This difference is chiefly due to the presence of salts, particularly potassium salts, in the blood, which render the combination between hæmoglobin and oxygen more unstable; when hæmoglobin is dissolved in water containing the same salts as those normally present in blood, its dissociation-curve is nearer to that of blood.

The other factors which alter the form of the dissociation-curve of blood are (1) the temperature of the blood, and (2) the presence of carbon dioxide or other acids. The higher the temperature of the blood and the greater the amount of carbon dioxide or other acids in the blood, the more readily does the oxyhæmoglobin dissociate. The effect of carbon dioxide and of lactic acid is shown in Fig. 82. These factors modify not only the *extent* to which oxyhæmoglobin dissociates at the same partial pressure

of oxygen, but also the *rate* at which it loses oxygen and becomes reduced. The greater ease with which the oxyhæmoglobin dissociates in these circumstances increases the amount of oxygen set free and therefore available for the tissues; and this effect will be especially marked and beneficial when the tissues are functionally active and are giving out large amounts of carbon dioxide and require a large supply of oxygen.

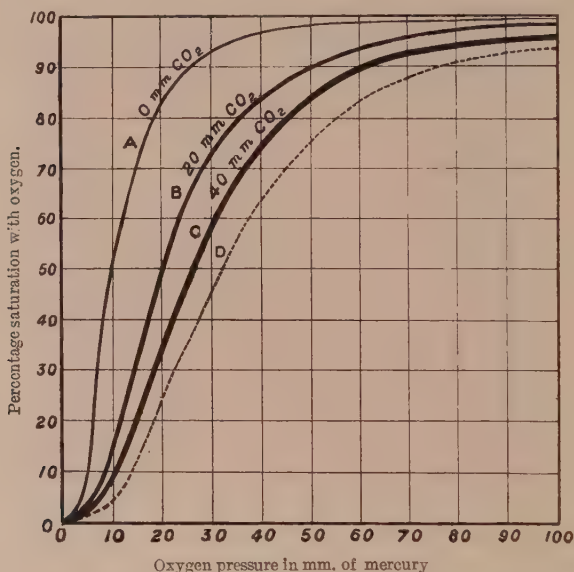


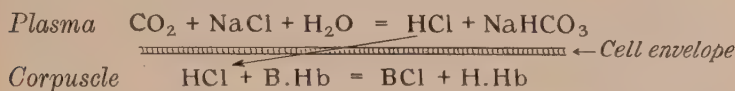
FIG. 82.—A, B, and C show the effect of varying tensions of CO_2 in blood on the dissociation-curve of oxyhæmoglobin. The dotted line D is the dissociation-curve of oxyhæmoglobin in blood to which 0.025 per cent. of lactic acid was added.

Although these conditions influence the rate of transference of oxygen from the blood to the tissues, they do not appreciably affect the amount of oxygen taken up by the blood as it passes through the lungs. The partial pressure of oxygen in the lungs is normally just over 13 per cent. (about 105 mm. Hg), and a consideration of Fig. 82 shows that at this pressure of oxygen the saturation of the blood will be practically the same, whether the blood is normal or whether it contains an excess of carbon dioxide or a trace of lactic acid.

CARBON DIOXIDE IN BLOOD.—The tension of carbon dioxide in blood is equal to a partial pressure of about 4 per cent.

of carbon dioxide. At this tension, if the carbon dioxide were simply dissolved in the blood, the latter would contain only about $2\frac{1}{2}$ volumes of carbon dioxide per 100 volumes of blood; but, since 100 volumes of blood, when exposed to a vacuum or treated with acid, give off from 45 to 50 volumes of carbon dioxide, most of this must be in a state of chemical combination.

THE CHLORIDE SHIFT.—The greater part of the carbon dioxide of blood is carried by the plasma in the form of sodium bicarbonate. There is a further fluctuating amount of CO_2 carried by the blood, because of the existence of a curious chemical interchange which was discovered by Hamburger. The hæmoglobin of the red cells is a feeble acid capable of combining with potassium. When carbon dioxide enters the plasma from the tissues, it reacts with NaCl of the plasma to form sodium bicarbonate with the liberation of HCl thus:—



The HCl at once penetrates the red blood-cells, the sodium bicarbonate remains behind in the plasma. Inside the cells the HCl reacts with the hæmoglobin-potassium compound to form KCl and free hæmoglobinic acid. Hence it is seen that when CO_2 is added to the blood the bicarbonate concentration in the plasma rises and the chloride concentration of the plasma falls, while the chloride content of the red cells increases. The opposite changes occur when CO_2 is removed from the blood by exposing it to a lower partial pressure. The dissociation-curve of carbon dioxide in blood exposed to varying partial pressures of carbon dioxide has a form not unlike that for the dissociation of oxyhæmoglobin (Fig. 83); the dissociation is most rapid when the partial pressure of carbon dioxide varies from 0 to 30 mm. Hg. Now oxyhæmoglobin is a stronger acid than reduced hæmoglobin. It therefore tends to recover the potassium which was taken from it by the chloride shift. The HCl , therefore, has to diffuse out of the corpuscle back into the plasma, where it reacts with the bicarbonate, turning out the CO_2 and reforming NaCl . In consequence, oxygenated blood gives off its carbon dioxide more readily than deoxygenated blood, and the oxygenation of the blood as it flows through the lungs probably facilitates the escape of carbon dioxide from the blood into the alveolar air.

In man, the difference between the tension of carbon dioxide in venous blood and in alveolar air is probably about 6 mm. Hg.

This difference is much smaller than that between the tension of oxygen in alveolar air and venous blood respectively, but owing to its greater solubility in water carbon dioxide can traverse a moist membrane such as that separating the air in the lungs from

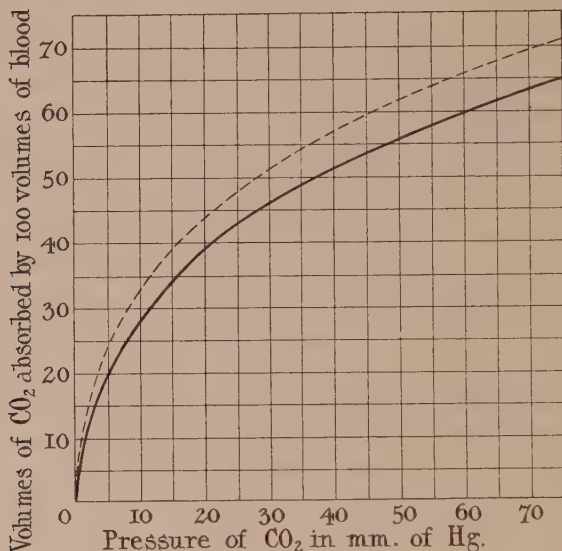


FIG. 83.—Dissociation-curve of CO₂ in blood.
(From Christiansen, Douglas and Haldane.)

Lower curve: blood exposed to CO₂ and air. Upper curve: blood exposed to CO₂ and hydrogen, i.e. deoxygenated blood.

the blood twenty-five times as quickly as oxygen; and the difference between the tension of carbon dioxide in venous blood and in alveolar air, slight though it is, is sufficient to allow the gas to pass from the blood into the air in the lungs by simple diffusion.

SECTION IV

THE REGULATION OF THE RESPIRATORY MOVEMENTS.

Oxygen is continually passing from the alveolar air into the blood, and is replaced by the entrance of air from the atmosphere during respiration. Similarly, carbon dioxide is constantly diffusing from the blood into the alveolar air, and with each expiration some of this is expelled from the lungs. Assuming that the amount of air entering and leaving the lungs with each breath is 400 c.c., and that the expired air contains 4 per cent. of carbon dioxide, then, with each respiration, 16 c.c. of carbon

dioxide are removed from the body. Since the composition of alveolar air is nearly constant, it is evident that 16 c.c. of carbon dioxide must, in the same time, have passed from the blood into the alveolar air. When carbon dioxide is formed more rapidly in the body and taken up by the blood, it passes into the alveolar air and tends to raise the percentage of carbon dioxide in alveolar air above the normal. Hence, if the percentage of carbon dioxide in alveolar air is to remain constant, as it nearly does under normal conditions, at constant atmospheric pressure, the amount of air passing into and out of the lungs at each breath must be correspondingly increased. Thus if 32 c.c. of carbon dioxide pass from the blood into the alveolar air, during a breath, the standard percentage of 4 for the CO_2 can still be preserved by increasing the air taken into the lungs from 400 c.c. to 800 c.c. In the same way, the need of the body for more oxygen is met by a larger amount of air entering the lungs at each inspiration. This process, whereby any accumulation of carbon dioxide or deficiency of oxygen, in the alveolar air, and consequently in the blood, is prevented, is under the control of the central nervous system, and is regulated in such a way that an excess of carbon dioxide, or a lack of oxygen, leads to deeper and more frequent respiratory movements.

The rhythmic alternation of inspiration and expiration is brought about by the contraction and relaxation of the respiratory muscles, which are controlled and co-ordinated by the respiratory centre.

THE RESPIRATORY CENTRE.—The centre is bilateral, the two halves being connected by commissural fibres, each half controlling the muscles of the corresponding side. Its position has been determined by observing the effect upon the respiratory movements of transection of the brain-stem or spinal cord at various levels. Recent observation indicates that the centre extends along almost the whole length of the fourth ventricle. When a section is made through the brain-stem at any point above the level of the fourth ventricle, respiration is unaffected. A section made a little below this point causes some slowing of respiration; transection at, or just below, the level of the *striæ acusticæ* leads to pronounced changes in respiratory rate and rhythm. If the spinal cord is divided at the upper end of the cervical region, the respiratory muscles supplied by nerves above the section, *e.g.* those which dilate the *alæ nasi*, continue to contract. Destruction of the medulla oblongata in the region of the apex of the *calamus scriptorius* is at once followed by cessation of all respiratory movements. The region occupied by the centre

is not sharply defined, but it is undoubtedly closely connected with the sensory nuclei of the vagus nerves.

There is no evidence of the existence of subsidiary centres in the spinal cord.

The centre continues to send out rhythmic impulses to the respiratory muscles when it is cut off from afferent impulses reaching it either from the higher parts of the brain or from the spinal cord. If, however, the brain-stem is divided below the pons, and the vagus nerves are also divided, the respiratory movements are replaced by a series of inspiratory spasms, and the animal dies after a short time. It is doubtful, therefore, whether the centre can be regarded as acting automatically in the absence of all afferent impulses, though this view has been taken by some writers.

The question is one of theoretical rather than practical interest, since, in ordinary circumstances, a constant stream of afferent impulses is reaching the centre and modifying its activity; and hardly any nervous centre in the body is more easily influenced in this way than the respiratory centre. For instance, the mere directing of one's attention to the respiratory movements is sufficient to alter their rate or depth. The respiratory centre, like the vaso-motor centre, is also extremely sensitive to any changes in the composition of the blood supplying it. These two factors which modify its activity, namely, (1) the composition of the blood and (2) nervous impulses from the higher centres or from the peripheral nerves, will be considered separately. The former affects primarily the depth, and the latter the rate, of respiration.

THE TENSION OF CO₂ IN THE BLOOD.—The two most important changes in the composition of the blood which alter the respiratory movements are: (1) variations in the tension of carbon dioxide, and (2) a fall in the tension of oxygen. If a man is allowed to breathe air containing 2 to 3 per cent. of carbon dioxide the respiratory movements become much deeper, and after a time somewhat more frequent; such an experiment is illustrated in Fig. 84. It is further found that the percentage of carbon dioxide in the alveolar air remains almost unchanged. The immediate effect of breathing air containing an excess of carbon dioxide is to increase the percentage of that gas in the alveolar air, thereby diminishing its passage by diffusion from the blood into the air in the lungs. As a result, the tension of this gas in the blood rises slightly; the increase in tension stimulates the respiratory centre to greater activity, and the amount of air passing into and out of the lung with each breath may be doubled or trebled.

In this way a larger amount of carbon dioxide is expelled from the lungs with each expiration, and the mean tension of this gas in the alveolar air is thereby kept almost at its normal level.

The effect of carbon dioxide in stimulating the respiratory centre is also seen in muscular exercise, during which the



FIG. 84.—The effect of CO_2 on the respiratory movements in the normal animal.
The inspired air contained 3 per cent. CO_2 during the period marked on the tracing.

muscles form a large amount of carbon dioxide, which passes into the blood and raises the tension of this gas in the blood. This rise in tension stimulates the respiratory centre, and the respiratory movements become deeper and more frequent, with the result that a larger amount of carbon dioxide is carried off in the expired air. The response of the respiratory centre to the stimulus of carbon dioxide is so delicately adjusted that the tension of carbon dioxide in the blood and alveolar air rises but little during exercise. In one series of experiments the following figures were obtained :—

	Percentage of CO_2 in Alveolar Air.	Tension of CO_2 in Blood.
Rest	5.6	46
Exercise	6.1	58

Since the slightest rise in the tension of carbon dioxide in the blood increases the respiratory movements, a diminution may be expected to lessen the respiratory movements by diminishing or abolishing the stimulus to the centre. When an individual takes a number of deep breaths (forced respiration), more carbon dioxide is removed from the lungs than is entering them from the blood. Hence the tension of carbon dioxide in alveolar air, and in blood, falls to such a level that it no longer stimulates the

respiratory centre, and respiration ceases for a short time (apnœa). (See later.)

THE H ION CONCENTRATION OF THE BLOOD.—It is clear that the activity of the respiratory centre and, consequently, the amount of air passing into and out of the lungs is dependent on the tension of carbon dioxide in the blood. It has been pointed out, however (p. 73), that the reaction of the blood, that is to say, its H ion concentration, depends almost entirely on the relative amount of dissolved carbon dioxide and of sodium bicarbonate present in the blood-plasma. This relationship can be expressed by the equation:—

$$H_O \text{ (H ion concentration)} = \frac{K^* \times H_2CO_3}{NaHCO_3}$$

Since the amount of carbon dioxide dissolved in the plasma varies directly with the tension of carbon dioxide in the blood, it is clear that every change in the tension of carbon dioxide will alter the reaction of the blood, provided the amount of bicarbonate remains constant. If the tension of carbon dioxide rises, the blood will tend to become acid, whereas if the tension falls, the blood will become more alkaline. It has, in fact, been shown that the carbon dioxide dissolved in the plasma stimulates the respiratory centre, probably in a specific manner, or else because, being an acid, it increases the concentration of hydrogen ions in the blood. It is probable that the cells of the respiratory centre are exquisitely sensitive to a change in hydrogen ion concentration however produced, but that carbon dioxide acts as a specific stimulus because it can more readily penetrate the cells.

It follows that the addition of any acid to the circulating blood will lead to greater activity of the respiratory centre. If, for example, 0·02 to 0·04 per cent. of lactic acid is rapidly added to the blood, it neutralises part of the sodium bicarbonate of the plasma, setting free CO_2 . The respiratory centre is at once stimulated and the breathing becomes more vigorous until sufficient carbon dioxide has been removed from the blood to restore the normal ratio; the reaction of the blood is then normal although it contains less carbon dioxide and sodium bicarbonate than usual.

It may be concluded, then, that the activity of the respiratory centre is normally evoked and controlled by the carbon dioxide concentration of the blood; when this exceeds a certain level, respiration becomes more vigorous, and when it falls below this level apnœa occurs. The centre is so sensitive that the slightest

* K is a constant.

rise in the free carbon dioxide concentration of the blood leads to hyperpnœa, which continues until sufficient carbon dioxide has been removed from the body to bring back the reaction of the blood to its normal level, and a fall in the carbon dioxide concentration decreases or abolishes the respiratory movements until the blood regains the CO_2 concentration necessary to excite the respiratory centre and evoke normal quiet breathing.

ACAPNIA.—Carbon dioxide is essential for maintaining the tone of medullary and of spinal vaso-motor centres. If prolonged excessive ventilation of the lungs be carried out, the carbon dioxide pressure is greatly lowered, and the vaso-motor centres are depressed; fall of arterial blood-pressure and dizziness result. This condition, called *acapnia*, is at once remedied by the administration of air containing 3 or 4 per cent. of carbon

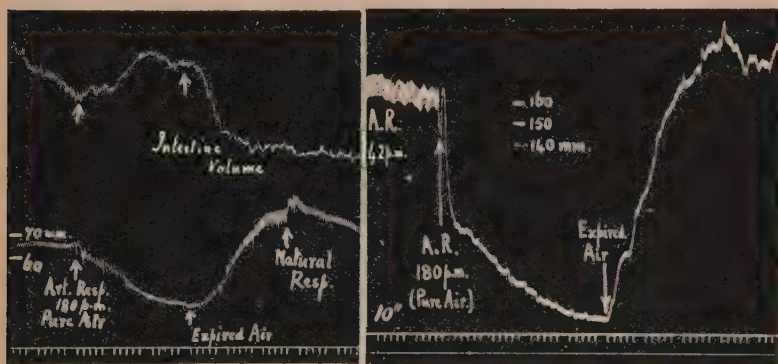


FIG. 85.—Effect of excessive pulmonary ventilation on arterial pressure of decerebrate cat. At the first arrow, artificial respiration with air was carried out at the rate of 180 inflations per minute; at the second arrow, the inflation was continued but with human expired air containing about 4 per cent. of CO_2 . (Dale and Evans.)

dioxide, even if the forced respiration is continued (Fig. 85; see also p. 143). Another very important, though less delicate means by which the reaction of the blood is kept within its proper limits is by the excretion by the kidney of proper proportions of acid and base. (See p. 16 and Chapter XXI.)

THE TENSION OF OXYGEN IN THE BLOOD.—The normal tension of oxygen in alveolar air is 105 to 110 mm. Hg. At this tension the blood leaving the lungs is almost fully saturated with oxygen, and the dissociation-curve of blood (p. 180) shows that,

even when the oxygen tension is reduced to 70 mm. Hg, the blood still contains 90 per cent. of its hæmoglobin as oxyhæmoglobin. Experiment shows, in fact, that atmospheric air containing only 12 to 13 per cent. of oxygen, which corresponds with about 8 per cent. of oxygen in the alveolar air, can be breathed without discomfort and without any alteration in the respiratory movements.

EFFECT OF OXYGEN WANT.—When the percentage of oxygen in alveolar air falls below 8 per cent. the breathing often becomes deeper and considerable hyperpnœa may be produced. At the same time the individual becomes cyanosed and may feel giddy, or may even lose consciousness. These symptoms are the result of the imperfect oxygenation of the blood. The mere lack of oxygen may in itself act as a stimulus to the respiratory centre, or it may render the respiratory centre more sensitive to the stimulus furnished by the carbon dioxide so that it can be excited by a smaller tension of carbon dioxide in the blood than that normally present. Hence, if the tension of carbon dioxide in the blood is normal, it stimulates the abnormally excitable centre very strongly, and hyperpnœa occurs. In the second place, if the lack of oxygen is at all prolonged, lactic acid appears in the blood. Lactic acid is normally formed in the body, and, in the presence of an adequate supply of oxygen, it is subsequently oxidised to carbon dioxide and water; when the supply of oxygen is insufficient the lactic acid passes into the blood and, by setting free carbon dioxide, stimulates the respiratory centre, and the respiratory movements become deeper. The deeper breathing raises the tension of oxygen in the alveolar air, and thus increases the amount of oxygen which can be taken up by the blood. In one experiment, for example, the inspired air contained 11·6 per cent. of oxygen, which would correspond (if no hyperpnœa occurred) with 5 per cent. of oxygen in the alveolar air; but the respiratory movements increased to such an extent that the alveolar air actually contained 6·8 per cent. of oxygen. Hence hyperpnœa helps to protect the tissues from the ill effects of a lack of oxygen in the inspired air.

EFFECT OF OXYGEN EXCESS.—The presence of an excess of oxygen in alveolar air has no effect on the respiratory movements, and wide variations may occur in the partial pressure of oxygen in the alveolar air without any appreciable change taking place in the respiration; even when pure oxygen is breathed for a short time, respiration is unchanged in a healthy individual. It is evident, therefore, that, provided the supply of oxygen is adequate, the depth of the respiratory movements is normally regulated by

the tension (partial pressure) of carbon dioxide in the alveolar air and in the blood.

EFFECT OF CHANGES IN PARTIAL PRESSURE OF OXYGEN AND CARBON DIOXIDE

	Barometric Pressure.	Percentage of CO ₂ in Dry Alveolar Air.	Percentage of O ₂ in Dry Alveolar Air.	Alveolar Pressure of CO ₂ in Percentage of an Atmosphere.	Alveolar Pressure of O ₂ in Percentage of an Atmosphere.
1	646.5 mm. Hg	6.61	13.19	5.23	10.41
2	755 ,,	5.95	13.97	5.53	13.06
3	1260 ,,	3.52	16.79	5.84	28.84

Further, this tension is extremely constant in the same individual, though, as shown in the foregoing table, the actual percentage of carbon dioxide in the lungs varies with the barometric pressure. For example, when the barometric pressure is 1260 mm. Hg, the alveolar air contains 3.52 per cent. carbon dioxide ; this represents a partial pressure of $\frac{3.52 \times 1260}{100}$
 $= 44.4$ mm. Hg, $= 5.84$ per cent. at 760 mm. Hg pressure.

ASPHYXIA.—The effects of lack of oxygen in the blood are seen in their most extreme form in asphyxia, and affect not only the respiratory but also the circulatory system. Asphyxia may be brought about by occlusion of the trachea, by the absence of oxygen in the air breathed, and in other ways. Three stages are usually described.

(1) **THE STAGE OF HYPERPNEA.**—During this period, which lasts from half to one minute, the respiratory movements gradually increase in depth, and soon involve not only the muscles usually employed in respiration, but also the accessory muscles. The respiratory movements during this stage are co-ordinate, and show an alternate inspiratory and expiratory rhythm. Consciousness is lost at the end of this stage ; the expiratory movements become more and more exaggerated, and the first stage passes into

(2) **THE STAGE OF EXPIRATORY CONVULSIONS.**—During this period every muscle which can assist expiration is called into action, and at the same time convulsive movements of the limbs take place. This period lasts about one minute, and is succeeded by

(3) **THE STAGE OF EXHAUSTION,** during which the animal lies passive, the muscles are flaccid except for an occasional deep inspiration, the pupils are widely dilated, and all reflexes are absent.

Death takes place from three to four minutes after the onset of asphyxia. The blood after death is almost free from oxygen.

THE SEQUENCE OF EVENTS IN ASPHYXIA.—At the outset, carbon dioxide accumulates in the blood and excites the respiratory centre, producing hyperpnœa. Towards the end of the first stage the increasing deficiency of oxygen begins to make itself felt, leading to still greater activity of the respiratory centre and to loss of consciousness. In the second stage, the lack of oxygen increases the excitability of the whole of the central nervous system, giving rise to the general convulsions which are observed; this effect is soon succeeded by paralysis, resulting from the prolonged deficiency of oxygen, and ending in death. All these effects are most pronounced when the supply of oxygen is cut off abruptly and completely; if the lack of oxygen is brought about gradually, the respiratory changes may be comparatively slight. The same sequence of events may be observed even if, during asphyxia, there is no mechanical obstruction to the escape of carbon dioxide from the lungs and therefore no *actual* increase of this gas in the blood. In these circumstances the hyperpnœa is due to the greater excitability of the respiratory centre, which is produced by acute and extreme lack of oxygen.

The vascular changes are also caused partly by excess of carbon dioxide and partly by lack of oxygen, as is shown in Figs. 86 and 87. These tracings make it clear that a rise of blood-pressure similar to that seen in asphyxia (Fig. 86, A) is produced either when the animal is allowed to breathe a gas containing no oxygen and no excess of carbon dioxide (Fig. 86, B), or when it breathes air containing an adequate supply of oxygen and a large excess of carbon dioxide (Fig. 87, A), or, finally, when lactic acid is injected into the circulation (Fig. 87, B).

The rise of arterial pressure is due to stimulation of the vaso-motor centre, which produces general constriction of the arterioles; adrenaline also is set free into the blood-stream, and contributes to the rise of pressure. By enclosing a loop of intestine in a plethysmograph it may be shown that, with the onset of asphyxia, the volume of the loop diminishes owing to constriction of its blood-vessels, and that this constriction persists until the death of the animal. The final fall of blood-pressure must be due, therefore, to failure of the heart; owing partly to the resistance offered by the high blood-pressure, partly to the direct effect of lack of oxygen upon the nutrition of the heart itself, the heart gradually diminishes its output, it becomes more and more dilated, and finally ceases to beat. When the vagus nerves

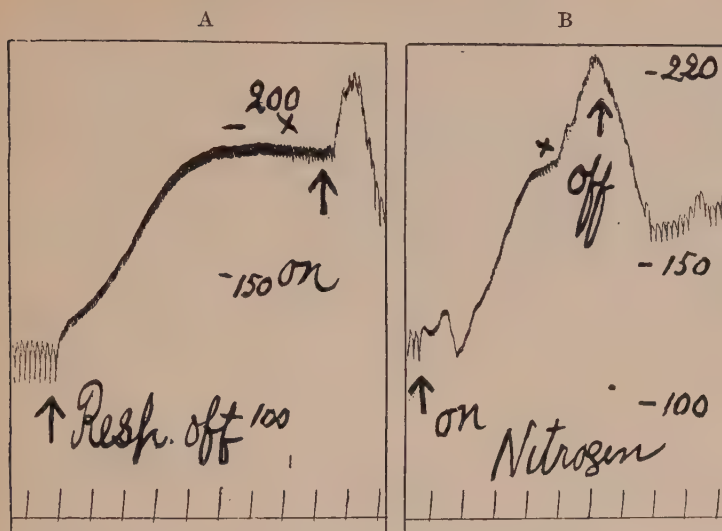


FIG. 86.—Tracing of arterial pressure. (Mathison.)

A shows the effect of asphyxia; B shows the effect of breathing pure nitrogen. The figures represent arterial pressure in mm. Hg.

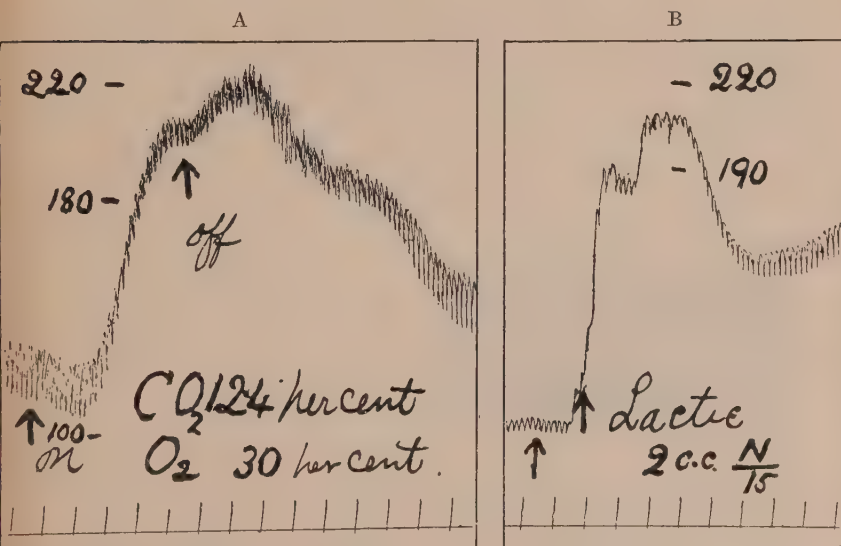


FIG. 87.—Tracing of arterial pressure. (Mathison.)

A shows the effect of excess of CO₂ in inspired air; B shows the effect of injecting lactic acid into the circulation.

are intact, the vaso-constriction leads to reflex slowing of the heart, and the rise of arterial pressure is smaller; the slowing of the heart lessens the strain thrown upon it, and life is prolonged for a minute or so longer. During asphyxia the conductivity of the auriculo-ventricular bundle is often diminished, producing a condition of heart-block, so that the auricles may beat twice or thrice as frequently as the ventricles. The increased activity of both the respiratory and vaso-motor centres in asphyxia is, undoubtedly, the result of increased H ion concentration in the blood; it must be noted, however, that the respiratory centre is the more sensitive, and may be excited by an excess of carbon dioxide too slight to affect the vaso-motor centre.

SECTION V

THE NERVOUS REGULATION OF RESPIRATION.—The respiratory centre can be influenced by nervous impulses reaching it (1) along the vagus, (2) from the higher parts of the brain, and (3) from other afferent nerves; the impulses affect primarily the frequency of the respiratory movements.

THE VAGUS NERVES.—The influence of the vagus nerves is most easily studied in the rabbit, by recording the movements of an isolated slip of the diaphragm (p. 171). When a record of the respiratory movements is obtained by this method, it may be seen that division of the vagus nerves is followed by a decrease in the frequency of respiration, although each breath is deeper than before. If, on the other hand, with the vagi intact, the lungs be filled and emptied by means of bellows the slip will be seen alternately to relax and expand. If, then, the bellows be stopped for a few seconds with the lungs full, the slip of diaphragm will be seen to

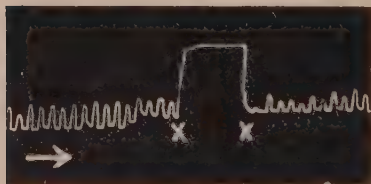


FIG. 88.—The tracing shows that an inflation of the lungs between X and X causes a relaxation of the diaphragm. Upstroke = relaxation.

stop in the relaxed condition, as shown in Fig. 88, that is, as it would be to bring about emptying of the lungs. If, however, the bellows be stopped at the end of inspiration with the lungs empty, the slip of diaphragm will be seen to contract as if to fill the lungs (see Fig. 89). The above is known as Head's experiment.

This experiment makes it clear, first, that the vagus nerves contain afferent fibres carrying impulses to the respiratory centre, which modify the rate of

respiration; and, second, that these impulses are of two kinds, one tending to cause inspiration and the other expiration. These fibres have their origin in the lungs, and their endings can be stimulated either by inflating the lungs, or by sucking air out of them.

It is evident that distension of the pulmonary alveoli stimulates the endings in the lungs of nerve-fibres

which pass up the vagus to the respiratory centre. These fibres convey impulses which inhibit inspiration and bring about expiratory movements. On the contrary, collapse of the pulmonary alveoli stimulates the endings of nerve-fibres running up the vagi and conveying impulses to the respiratory centre whereby inspiratory movements are evoked.

The existence of such impulses can be further demonstrated by connecting the vagus with a string galvanometer. With each inspiration a deflection of the thread takes place, indicating the passage of an impulse along the nerve; a similar deflection may also be observed during expiration.

In normal respiration these two sets of fibres are alternately stimulated, each inspiration sending impulses along one set of fibres and reflexly causing expiration, whereas each expiration gives rise to impulses which bring about another inspiration. The electrical variations in the vagus seem to show that the impulses leading to expiration are the more important and more pronounced.

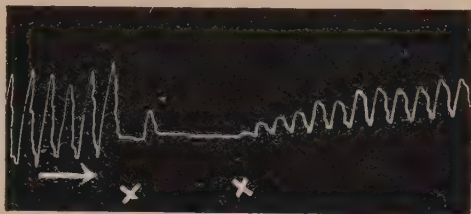


FIG. 89.—The tracing shows that a deflation of the lungs between X and X causes a contraction of the diaphragm. Downstroke = contraction.

EFFECTS OF DIVISION OF VAGI.—Although vagal impulses help to maintain the normal rhythm of the respiratory movements, respiration continues after they are prevented from reaching their respiratory centre by division of the vagi. Their principal function seems to be that of rendering the centre more sensitive to the normal stimulus of carbon dioxide, and of controlling the strength of the impulses sent out from the respiratory centre to the respiratory muscles. In their absence, the respiratory centre is not stimulated until the tension of carbon dioxide in the blood rises higher than in the normal animal, although each respiration, when it does occur, is exceedingly forcible.

Further, after division of the vagi, the normal adjustment of the respiratory movements in response to any considerable

increase in the tension of carbon dioxide in alveolar air and blood is no longer efficiently carried out. During muscular exercise, for example, a normal animal breathes not only more deeply, but also more frequently, and is thus able to expel from the lungs almost all the additional carbon dioxide reaching them from the blood; after section of the vagi the *rate* of respiration remains unaltered, the ventilation of the lungs becomes inadequate, and the percentage of carbon dioxide in the alveolar air rises. The same result is seen when an animal, with its vagi divided, breathes

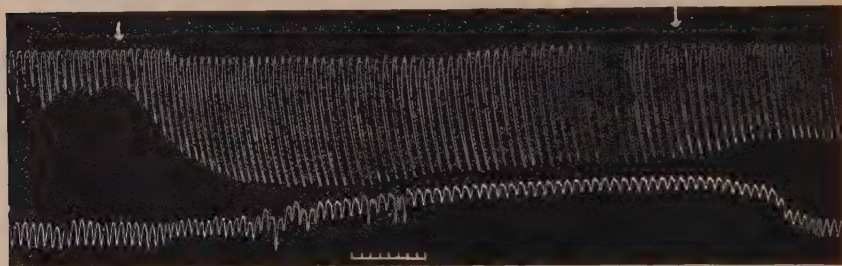


FIG. 90.—Respiratory movements in rabbit with vagi divided. Between the arrows the inspired air contained 10 per cent. CO_2 . Note that the *rate* of respiration is not increased. (Scott.)

air containing an excess of carbon dioxide (Fig. 90), the ventilation of the lungs being much less than in the normal animal, as is seen in the following table:—

VENTILATION OF THE LUNGS

Composition of Inspired Air.	Total Ventilation per Minute.	
	Normal Rabbit.	Rabbit with Vagi divided.
(1) Atmospheric air	1368 c.c.	1305 c.c.
(2) Air to which 8·6 per cent. CO_2 was added	2813 „	1596 „

IMPULSES FROM THE HIGHER PARTS OF THE BRAIN.—

In an anæsthetised animal the brain-stem may be divided at the level of the pons without any obvious change being produced in the respiratory movements. Nevertheless, impulses from the higher parts of the brain can greatly modify respiration, and the effect on respiration of emotions, such as anger or excitement, is often very marked.

Again, the respiratory movements become deeper and more

frequent at the very beginning of muscular exercise; even the first breath taken after the onset of muscular work is much deeper than the respiration during rest (Fig. 91). These changes

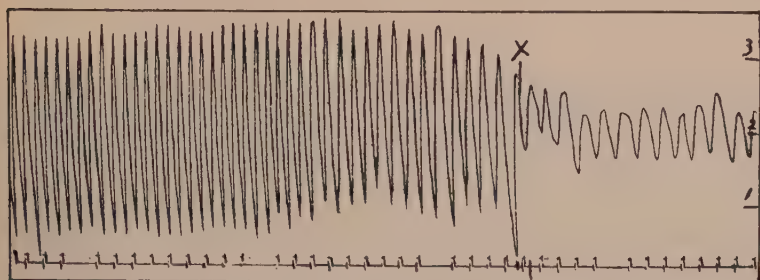


FIG. 91.—Effect of muscular work on the respiratory movements. (Krogh.)

The work begins at X. Tracing to be read from right to left.

occur too quickly to be brought about by an increase in the tension of carbon dioxide in the blood, and observation shows that they are due to impulses passing from the cerebral cortex to the respiratory centre, which render it more sensitive than before to the hydrogen ion concentration of the blood. Hence the normal tension of carbon dioxide, acting on the unusually excitable centre, calls forth deeper and more rapid respirations. By this means the amount of oxygen entering the lungs and passing to the blood and tissues is increased at the very beginning of exercise, and the muscles are able to take up from the blood, without delay, the additional oxygen which they need for their increased activity.

The respiratory movements may also be modified by impulses reaching the centre from almost every region of the body. Painful stimuli usually produce hyperpnœa, whereas impulses passing along the fifth nerve and the nerves from the upper respiratory passages tend to inhibit respiration; these nerves may be stimulated by irritant vapours, such as that of ammonia. The superior laryngeal nerve supplies sensory fibres to the glottis, and stimulation of its endings, for instance, by the entrance of a crumb into the glottis, inhibits inspiration and causes violent expiratory efforts. Electric stimulation of the central part of the divided nerve brings about the same effect.

APNŒA.—Reference has already been made to the inhibition of the respiratory movements, which is known as apnœa. The most important condition which gives rise to apnœa is a fall in the tension of carbon dioxide in the blood. This occurs whenever the ventilation of the lungs is increased without any corresponding

rise in the production of carbon dioxide in the body, and may therefore be brought about either, in man, by voluntary forced breathing (Fig. 92), or, in animals, by vigorous artificial respiration. In these circumstances the apnœa may last for one or two minutes, respiration beginning again as soon as the tension of

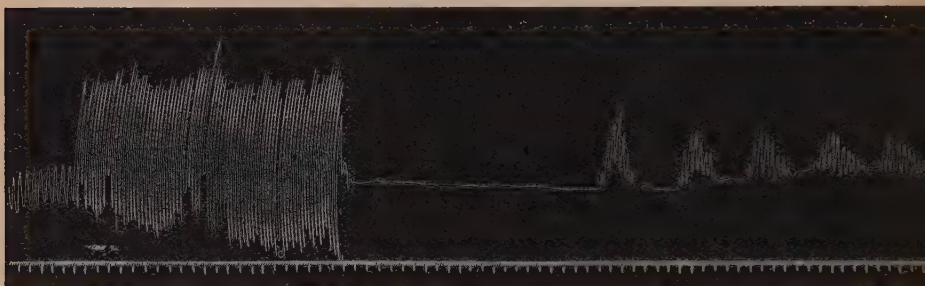


FIG. 92.—Forced breathing in man, followed by apnœa and subsequently by Cheyne-Stokes breathing. (Haldane and Douglas.)

carbon dioxide in the alveolar air returns to its normal level. That it is due solely to a fall in the tension of carbon dioxide is clearly shown by the fact that, when the inspired air contains an excess of carbon dioxide, forced breathing is not followed by apnœa.

A totally different form of apnœa is that produced by electric stimulation of the upper end of the vagus nerve. It is known as vagus apnœa. This is due to the stimulation of the fibres of the vagus which inhibit inspiration.

Apnœa also occurs during deglutition, and lasts for a few seconds; the afferent impulses pass along the glossopharyngeal nerve. The effect of this inhibition is to prevent particles of food being drawn into the lungs by an inspiratory act during the process of swallowing.

CHEYNE-STOKES BREATHING.—This form of breathing (Fig. 93), which is not infrequently observed in human beings living at high altitudes or suffering from various diseases, more especially those affecting the circulatory system, has the following characteristics. After an apnœic pause respiration begins, the breaths being shallow at first and gradually increasing in depth till they reach a maximum. They then become smaller, and in a short time cease altogether, being succeeded by a period of apnœa. Cheyne-Stokes breathing can also be produced experimentally in healthy persons as a result of prolonged forced breathing, as is seen in Fig. 92; the immediate effect of the forced breathing is a

period of apnœa, and, when breathing recommences, it often exhibits the periodic character just described.

The phenomenon is caused by *lack of oxygen* in the blood. During the period of forced breathing, the tension of carbon dioxide in the alveolar air falls considerably, leading to prolonged apnœa. During the apnœic period the amount of oxygen in the blood decreases, and the supply of oxygen to the respiratory centre becomes inadequate, the result being that the respiratory

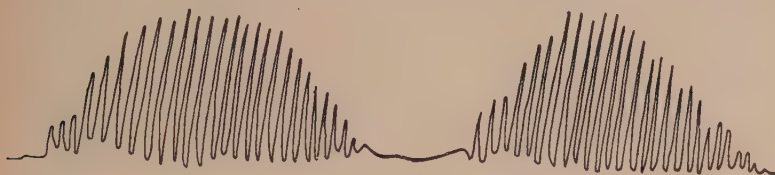


FIG. 93.—Cheyne-Stokes respiration.
(From *Practical Physiology*, by Pembrey and others.)

centre is rendered more excitable. At the same time the tension of carbon dioxide in the blood is slowly rising and eventually reaches a level which, although it is below that normally present in blood, is sufficient to stimulate the abnormally excitable respiratory centre. Respiration begins again, and the oxygen taken into the lungs and into the blood gradually lowers the excitability of the respiratory centre; at the same time the breathing removes some carbon dioxide from the lungs, the result being that the chemical stimulus to respiration disappears, and the breaths become smaller and finally stop. This sequence of events whereby periods of apnœa alternate with periods of respiration may recur many times, until finally the apnœic pauses disappear and normal breathing is resumed.

When this form of breathing occurs in disease, it can be remedied either by allowing the patient to breathe nearly pure oxygen, which improves the nutrition of the respiratory centre, or by the administration of air containing a slight excess of carbon dioxide, which, by raising the tension of this gas in the alveolar air and blood, increases the strength of the stimulus to the respiratory centre.

SECTION VI

THE EFFECT OF LOWERED BAROMETRIC PRESSURE.—

When a person ascends from near sea-level to a height of 5000 to 10,000 feet or more, he is apt to suffer from symptoms which are generally described as *mountain sickness*. These symptoms are headache, mental confusion, blueness of the lips, and nausea or vomiting. They may occur when the individual ascends to this height in a train, and are therefore not due to muscular exercise, although they may become more severe when exercise is taken. They are caused entirely by lack of oxygen. With increasing altitude the barometric pressure, and therefore the partial pressure of oxygen in the atmosphere and in the alveolar air, gradually falls; and when the alveolar pressure of oxygen, which is normally 105 to 110 mm. Hg, falls to about 60 mm. Hg, the symptoms just described make their appearance. Similar symptoms are produced in animals and in man when they are placed in closed chambers and the barometric pressure is gradually reduced. If the individual remains at a high altitude, the symptoms pass off in the course of a few days, and after a time exercise may be taken without their recurrence. The adaptation of the body to the altered conditions is brought about by changes in both the respiratory and vascular systems. In the first place, it has been found that, when a man has become acclimatised to residence at a high altitude (*e.g.* 14,000 feet), he breathes more deeply, even when resting, than when he lives at or near sea-level. Owing to the greater ventilation of the lungs, the partial pressure of carbon dioxide in the alveoli decreases, and that of oxygen rises. At a high altitude, when the alveolar oxygen-pressure is low, even a small rise in the partial pressure of oxygen appreciably increases the extent to which hæmoglobin can take up oxygen as the blood flows through the lungs. For example, if, as a result of the increased ventilation, the alveolar pressure of oxygen rises from 36 mm. Hg to 53 mm. Hg, the saturation of the hæmoglobin in the blood leaving the lungs may be increased from 65 per cent. to 85 per cent.

In the second place, in persons who remain at a high altitude for a long period, the number of red corpuscles and the percentage of hæmoglobin in the blood are gradually increased. In one series of observations, made at a level of 14,000 feet, the hæmoglobin in the blood rose in the course of some weeks from 15 per cent. to 19 per cent. (127 on Haldane's hæmoglobinometer scale). When the subject returned to a low level, the percentage of hæmoglobin rapidly fell to normal. Hence, the deficiency in

the amount of oxygen taken up by each red corpuscle in the lungs is made good by the larger number of red cells in the blood, with the result that, at least in the resting man, the *amount* of oxygen carried from the lungs to the tissues is much the same at high altitudes as at low levels.

The extent to which adaptation takes place varies in different individuals ; in many cases the supply of oxygen to the tissues is barely sufficient during rest, and exercise frequently leads to an inadequate supply of oxygen to the tissues and brings on mountain sickness. This occurs less readily, however, in the trained than in the untrained person, partly because the former uses his muscles more economically, and therefore his demands for oxygen are not so great.

THE EFFECT OF RAISED BAROMETRIC PRESSURE.—

Men engaged in the building of bridges or tunnels are often compelled to work in caissons, which are filled with compressed air to prevent the inrush of water. They suffer no inconvenience, and the respiratory movements are not affected, while they are in the caisson, even though the pressure may be three or four atmospheres. Under this pressure, however, the blood dissolves an increased amount of oxygen and nitrogen. If a man leaves the caisson and the pressure to which the blood and tissue-fluids are exposed is suddenly reduced to atmospheric pressure, most of the nitrogen, previously in solution, is evolved as bubbles, which may obstruct the flow of blood along the blood-vessels or through the heart, or, when set free in the tissues, may damage delicate structures such as nerve-cells. The symptoms caused by this obstruction, and known as *caisson disease*, are very varied, and include paralysis, severe abdominal pain, and collapse. The disease is prevented by allowing the man to pass from the caisson into a special air-chamber (air-lock), in which the pressure is gradually lowered to that of the outer air so as to prevent any sudden evolution of nitrogen.

CARBON MONOXIDE POISONING.—The affinity of carbon monoxide for hæmoglobin is about 300 times as great as that of oxygen (p. 62) ; and, when air containing even a small percentage of carbon monoxide is breathed, the oxyhæmoglobin is replaced by carbon monoxide hæmoglobin, the supply of oxygen to the tissues is cut off, and asphyxia is produced. The fatal effects of breathing air containing coal-gas, in which carbon monoxide is present, are brought about in this way. Death may

often be prevented by the administration of oxygen, which not only increases the amount of oxygen dissolved in the blood and carried to the tissues, but, by its mass action, gradually displaces the carbon monoxide from its combination with hæmoglobin. Efforts should also be made to keep the patient warm. If to the oxygen 5 per cent. CO_2 be added, respiration is accelerated and the CO_2 more rapidly excreted. CO may be detected in the blood by means of the Reversion Spectroscope.

RESPIRATORY MOVEMENTS ON THE CIRCULATION.—

A tracing of the arterial pressure often shows oscillations corresponding with each respiratory movement, the pressure rising a little during inspiration and falling during expiration. Further, the pulse is more frequent during inspiration and less frequent during expiration (Fig. 94). The difference in the pulse-rate is

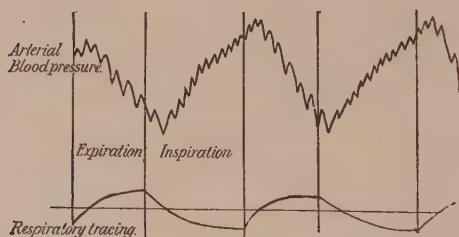


FIG. 94.—Effect of respiratory movements on arterial blood-pressure. (From Starling's *Principles of Physiology*.)

due to a slight diminution of the tone of the vagus during inspiration, which allows the heart to beat more rapidly: it is abolished by section of the vagi, but the respiratory oscillations of the blood-pressure are not affected by this procedure.

At the end of expiration, the pressure inside the cavity of the chest is slightly below atmospheric pressure, and the pressure on the walls of the great veins and of the heart is negative, whereas the pressure in the jugular vein in the neck, for example, is slightly higher than that of the atmosphere. Owing to this difference of pressure in the vessels within and outside the chest, blood tends to be sucked along the great veins and into the heart. With each inspiration the degree of negative pressure is increased, and the flow of blood into the heart becomes more rapid. The thin-walled auricles are also slightly dilated by the negative pressure, and the flow of blood to the heart is thus further assisted, the thick-walled ventricles and arteries being practically unaffected. As the result of the additional blood reaching the heart during inspiration, the amount of blood expelled from the heart at each beat becomes larger, and the arterial pressure rises.

A second factor which conduces to the inspiratory rise of arterial pressure is the descent of the diaphragm during inspiration; this, by diminishing the size of the abdominal cavity, raises

the intra-abdominal pressure and squeezes blood out of the abdomen along the inferior vena cava into the heart.

In man, the alterations in blood-pressure produced by the respiratory movements are of very complex origin, and the effects are not so constant as those just described for animals; they vary with the type of respiration, a purely costal inspiration causing a fall, and a diaphragmatic inspiration causing a rise, of blood-pressure.

SECTION VII

TISSUE-RESPIRATION.—The processes of external respiration, which have been thus far considered, are so adapted that the blood, when it reaches the capillaries, is almost fully saturated with oxygen. The essential process of respiration, however, is internal or tissue-respiration, which consists in the transference of oxygen from the blood to the tissues and the passage of carbon dioxide from the tissues to the blood.

Oxygen passes from the blood to the tissues by diffusion, and the amount which is available for the tissues depends largely upon the extent to which oxygen is set free in the plasma by the dissociation of oxyhæmoglobin. Since the tissues usually contain but little *free* oxygen, the conditions during the passage of the blood along the capillaries are almost the same as if it were exposed to a vacuum and, if sufficient time were available, the dissociation of oxyhæmoglobin in the capillaries would be nearly complete. But the time spent by any one portion of the blood in traversing the capillaries is short, and the blood normally gives up only about a third of its oxygen to the tissues, so that the mixed venous blood is approximately two-thirds saturated with oxygen.

If the rate at which the blood flows through an organ is increased, less time is available for dissociation of the oxyhæmoglobin in any one portion of the blood, although the *total* amount of oxygen taken up by the tissue may be unchanged. In these circumstances, the blood leaving the organ will be less venous than usual. On the contrary, if the blood-flow is unchanged but the *rate* at which oxyhæmoglobin can dissociate becomes more rapid, the blood, as it traverses the capillaries, will give up more oxygen than usual. The rate at which oxyhæmoglobin dissociates is increased by the addition to the blood of more carbon dioxide or of other acids, such as lactic acid, as it passes along the capillaries.

Greater functional activity of an organ is accompanied not only by a larger blood-flow and by the opening up of capillaries

previously closed but also by more rapid dissociation of oxyhæmoglobin as the blood traverses the organ, and the combination of these two processes greatly increases the amount of oxygen available for the needs of the active organ.

Guinea-pig's Muscles.	O ₂ per minute per grain.	No. of Capillaries per c.mm.	Oxygen-pressure in Capillary minus that in muscle.
Rest.	0·5	31	0·45
Massage	0·5	1400	0·04
Work	5	2500	1·4
Maximum circulation	10	3000	1·2

The above results obtained by Krogh show all these points extremely well, and particularly interesting is the last column, which shows how nearly the oxygen-pressure in the muscle comes to that in the capillary.

Carbon dioxide also passes by diffusion from the tissues, in which its tension is high, into the plasma, in which its tension is much lower. The tension of carbon dioxide in the tissues has been ascertained indirectly by measuring its tension in bile or urine, and is about 8 to 9 per cent. of an atmosphere, whereas its tension in blood is only 5 to 6 per cent. of an atmosphere.

THE CONSUMPTION OF OXYGEN BY THE TISSUES.—The tissues are constantly taking up oxygen, and the amount used by

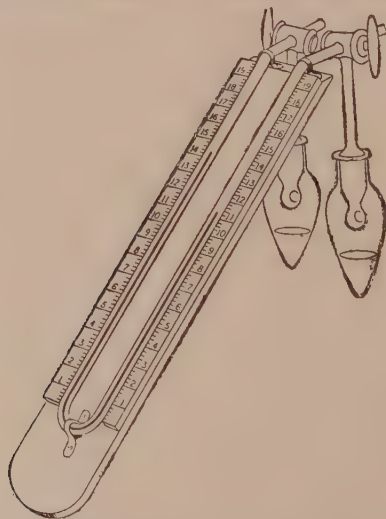


FIG. 95.—Barcroft's blood-gas apparatus. (From Barcroft's *Respiratory Function of the Blood.*)

any organ, for example the kidney, can be determined by ascertaining, first, the difference in the quantity of oxygen present in 1 c.c. of the blood entering and leaving the organ respectively ; second, the amount of blood flowing through the organ in a given time ; and, third, the weight of the organ. The degree to which the blood is saturated with oxygen is measured by suitable blood-gas apparatus, *e.g.* that shown in Fig. 95. The rate of blood-flow through the organ is ascertained by observing directly the quantity escaping from its vein in a given time. To take an example, if 1 c.c. of arterial blood contains 0.18 c.c. oxygen, and 1 c.c. of blood from the renal vein contains 0.13 c.c. of oxygen, each c.c. of blood passing through the kidney loses 0.05 c.c. oxygen. Supposing the rate of blood-flow through the kidney to be 50 c.c. per minute, the amount of oxygen taken up by the kidney is 2.5 c.c. ; and if the weight of the kidney is 30 grammes, 1 gramme of kidney uses 0.08 c.c. oxygen per minute. Experiments made in this way show that the amount of oxygen consumed by the different tissues of the body varies greatly ; the heart and kidney use (per gramme) more oxygen than any other organ.

O₂ CONSUMED BY 1 GRAMME OF TISSUE PER MINUTE

	Resting.	Active.
Skeletal muscle	0.003 c.c.	0.03 c.c.
Heart-muscle	0.05 c.c.	0.2 c.c.
Kidney	0.03-0.06 c.c.	0.15 c.c.
Submaxillary gland	0.023 c.c.	0.089 c.c.

CONTROL OF OXYGEN USED.—The amount of oxygen consumed by any organ in a given time is primarily determined by the organ itself, and, provided that the flow of blood to an organ is

OXYGEN CONSUMED BY THE SUBMAXILLARY GLAND

	Oxygen used by 1 Gramme of Gland per Minute.	Rate of Blood-flow through the Gland in c.c. per Minute.
(1) Resting	0.023 c.c.	0.35 c.c.
(2) Resting, with dilated blood- vessels.	0.024 „	3.5 „
(3) During the secretion of saliva	0.11 „	...

sufficient to supply it with the oxygen which it needs, a further increase in the oxygen content or flow of blood through it does not increase its consumption of oxygen. For instance, the rate

of blood-flow through the resting submaxillary gland may be increased tenfold without any rise taking place in the oxygen-consumption of the gland. The consumption of oxygen rises, however, whenever the functional activity of a tissue becomes greater, and, in the case of skeletal muscle, it may be increased tenfold during and just after muscular contraction. A similar rise occurs when the heart does more work, or when the secretory activity of the submaxillary or other glands is evoked.

The increased consumption of oxygen takes place not only during the period of secretion or of muscular work, but for some time after this is over (Fig. 96); and the oxygen is apparently

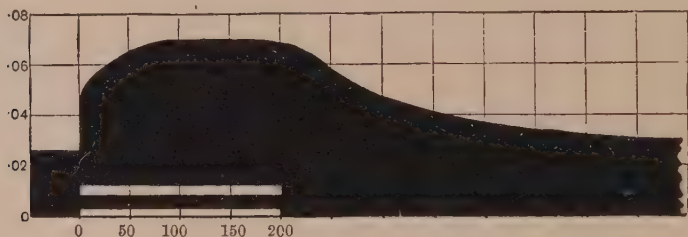


FIG. 96.—Ordinate = volume of oxygen used in c.c. per minute; abscissa = time in seconds; upper signal = duration of flow of saliva; lower signal = duration of chorda stimulation. Blackened area represents the oxygen used by the salivary gland. (From Barcroft's *Respiratory Function of the Blood*.)

used mainly in the carrying out of chemical changes whereby the gland or muscle stores up potential energy and is restored to its previous condition. It must be distinctly understood that the usage of oxygen, though indispensable for providing the energy for cell activities, may be dispensed with in the preliminary stages, *e.g.* an oxygen debt may be incurred. Thus, as was explained in the chapter on Muscle (p. 35), muscular contraction is brought about by the liberation of lactic acid, and oxygen plays no part. The function of oxygen is to oxidise a part of the lactic acid so formed and to enable the remainder to be reformed into hexose phosphate (lactacidogen). This important subject will be dealt with in further detail in Chapter IX, Exercise and Work.

The oxidative changes in the body normally take place in the tissue-cells and not in the blood itself. Hence portions of surviving tissue free from blood continue to respire if kept warm and moist and suspended in a fluid containing oxygen.

MECHANISM OF TISSUE OXIDATIONS.—There are various ways in which oxidations may occur in the tissues. The enzymes called *oxidases* are believed to act by causing union of the substance

to be oxidised with oxygen from the blood. But many tissue oxidations are really brought about in the first instance by the oxygen of water, and oxygen in the free state is only indirectly employed. For these indirect *oxydo-reductions* as they are called, four things are necessary, viz. : (1) a substance (X) to be oxidised, (2) a catalyser which brings about the reaction, (3) a substance (R) which can be reduced, *i.e.* which will take up temporarily the hydrogen from the water, and (4) (since an oxygen debt has been incurred) free oxygen to oxidise the reduced substance so that it can be used again. The reaction proceeds in the following stages :—

- (1) $X + H_2O = XO + H_2$ (oxygen acceptor oxidised).
- (2) $H_2 + R = RH_2$ (hydrogen acceptor reduced).
- (3) $2RH_2 + O_2 = 2R + 2H_2O$ (hydrogen acceptor oxidised).

If free oxygen is absent, the reaction stops at (2), with the result that X is oxidised (by the O of water) and R is reduced (by the H of water). Milk contains a catalyser called the Schardinger enzyme, capable of bringing about such changes. If to milk a little formaldehyde is added, and then a trace of methylene blue, the formaldehyde is oxidised to formic acid on warming, and the methylene blue is reduced to a colourless compound. On shaking with air the blue colour returns, and this may be repeated again and again until all the formaldehyde has been oxidised.

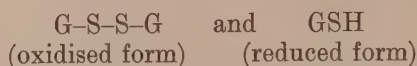
Fresh tissues also contain such catalysers, and also some substances capable of oxidation in this way.

When methylene blue is injected into an animal, and the animal is killed a few minutes later, the blood is coloured blue, whereas the tissues show no change of colour. This is because the tissues contain a substance which has become oxidised while the methylene blue has taken up hydrogen with the formation of a colourless reduction product. On exposing the tissues to the air, methylene blue is re-formed, and the tissues become deeply stained.

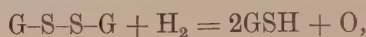
GLUTATHIONE.—All normal tissues, except blood, contain a substance which behaves in a similar manner to methylene blue in this respect. The substance, isolated by Hopkins, is called *Glutathione*, and is a dipeptide consisting of the two amino-acids, cystine and glutamic acid. The presence of glutathione may be demonstrated by grinding up a piece of fresh tissue (*e.g.* liver) with solid ammonium sulphate, adding a few drops of sodium nitroprusside solution, and then a few c.c. of dilute ammonia, when a purple colour is produced.

Glutathione can exist in an oxidised form in which two

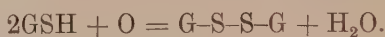
molecules of the dipeptide are linked together by sulphur atoms, and in a reduced form where the sulphur is present as an SH grouping:—



The oxidised form, under the influence of cell catalysors, can take up hydrogen of water and produce the reduced form of glutathione,



the oxygen of the water being used to carry out cell oxidations. The reduced form can take up free oxygen and give the oxidised form once more :—



HEXURONIC ACID.—Recently Szent-Gyorgyi has described a substance which forms a per-oxidase system, namely, hexuronic acid. This substance can be isolated from oranges, cabbages, and the cortex of the suprarenal glands. Molecular oxygen oxidises the substance irreversibly, forming new carboxyl groups. Copper accelerates and cyanide stops this action. On the other hand, it is rapidly reduced by animal tissues and by Hopkins' glutathione system. This substance would appear to play an important part in cell oxidation.

CYANIDE.—The extremely poisonous nature of cyanides and hydrocyanic acid is well known. Poisoning is due to the prevention of tissue oxidation, that is, oxygen is carried to the tissues by the blood and it diffuses into them as usual and yet its utilisations cannot take place. According to Warburg this is due to a chemical reaction between the cyanide and the small traces of free iron, or other metals, *e.g.* copper or cobalt, which normally play the highly important part of catalysts in tissue oxidation. The tissues may have a powerful avidity for oxygen; glutathione, hexuronic acid, and atmospheric oxygen may all be present and yet the combination may fail to take place if all the metal catalysts have been inactivated by cyanide.

CHAPTER IX

EXERCISE AND WORK

SECTION I

INCREASED ENERGY EXCHANGES.—The physiological processes which accompany the change from rest to activity have received a great deal of attention during recent years. The changes are many and complicated and affect directly or indirectly practically the whole body. That the performance of work is accompanied by increased energy exchanges is shown by the following figures :—

	Calories evolved as Heat.	Calories evolved as Work.
Rest	2397	none
Work	4574	546

In order to perform external work equal to 546 calories the body had to suffer increased energy exchanges amounting to 4574 — 2397 = 2177 calories. These appeared as heat. They represent the work done by the heart, lungs, central nervous system, etc., etc., in supplying the muscles with all that they require to enable them to do the external work of 546 calories.

INCREASED OXYGEN REQUIREMENT.—That additional oxygen is taken into the body via the lungs during activity is clearly shown by the results of many experimenters. The following values (Cathcart and Benedict) may be given as examples.

Condition.	C.c. Oxygen absorbed per Minute.
Lying down	243
Moderate work	1834
Severe work	3265

Values as high as 4000 to 6000 c.c. per minute have been obtained for men performing the most strenuous exercise for a short time. That is a nearly twenty-fold augmentation in the oxygen taken in per minute. A five-fold increase is quite common and may be

kept up for many hours. The fact that greater amounts of oxygen have been taken in by the body as a whole does not, without further evidence, conclusively prove that this additional oxygen has been taken up by the active tissues.

	Oxygen used, in c.c. per Minute, per Gramme of Tissue.	
	Resting.	Active.
Skeletal muscle	0·003	0·08
Unstriated muscle	0·004	0·007
Cardiac muscle	0·007	0·08
Liver	0·005	0·024
Salivary gland	0·027	0·089
Kidney	0·026	0·15
Suprarenal gland	0·045	0·13
Pancreas	0·03	0·10

The above table shows that active tissues require more oxygen than inactive ones.

THE OXYGEN INTAKE.—The intake does not rise instantaneously to its full value immediately the activity has begun. On the contrary, it increases at first rapidly, then more slowly to reach its full value. Similarly, the intake does not fall instantaneously when the activity is complete. On the contrary, it returns at first rapidly, then more slowly to reach its resting value.

INCREASED FOOD REQUIREMENTS.—That exercise increases the appetite is common knowledge, and also that a man performing hard muscular exercise requires more food than a resting man. The former may require $2\frac{1}{2}$ times the amount of food of the latter. Without additional evidence, however, this does not prove that the food has been utilised for providing the energy for activity. Proof rests on the following experiments: (1) glucose disappears from the fluid perfused through a beating mammalian heart (Lovatt-Evans); (2) the carbohydrate content of isolated skeletal muscle decreases as the result of activity; (3) all available evidence points to the same being true of cardiac muscle: it is for this reason that glucose is administered in heart failure; (4) it will be shown later that the respiratory quotient (CO_2 in c.c. expired divided by O_2 in c.c. used up), which is 1 for carbohydrate, 0·9 for protein, and 0·7 for fat, becomes almost exactly 1 during prolonged active exercise. This points to the utilisation of carbohydrate for the liberation of energy.

INCREASED CO₂ OUTPUT.—That carbon dioxide is evolved in increasing amount during activity is clearly shown by numerous experiments. The following values may be quoted as examples:—

Condition.	CO ₂ eliminated in c.c. per min.
Lying down	200
Moderate work	1720
Severe work	3227

In another case :

Rest without food	189·6
Rest with food	230·4
Work with carbohydrate food	705
Work with fat food	634·8

That this carbon dioxide which is leaving the body has actually left the active tissues is clearly shown by the analysis of the blood going to and coming from them.

	CO ₂ given out in c.c. per min.
Heart active	8·9
Heart poisoned by chloroform	1·9

In another experiment :

	CO ₂ given out in c.c. per gramme per min.
Heart normal	0·038
Vagus stimulated	0·005

At the beginning of exercise the voluntary respiratory effort and the quickening of the respiration by lactic acid from the muscles both cause CO₂ to be excreted in excess of oxygen absorbed. Temporarily respiratory quotients above 1·5 are sometimes met with. This fact will be referred to again later.

INCREASED OUTPUT OF BREAKDOWN PRODUCTS.—Of the breakdown products which are excreted in the urine, the following may be mentioned : lactic acid, creatinine, uric acid, and potassium. The appearance of traces of lactic acid in the urine almost always follows muscular exercise, if there has been an insufficient supply of oxygen. This lactic acid, as we have already seen, is derived from the hexose in combination with phosphoric acid as hexose phosphate (lactacidogen). When the muscles are active and the amount of oxygen is insufficient, this compound is broken up in increasing amount, and the lactic acid produced diffuses from the muscles into the blood. Some of this appears in the urine.

Creatinine is a normal constituent of the urine of meat eaters. But additional amounts invariably appear in the urine following hard exercise. This may come from the phosphagen of the worker's own muscles. Since both lactacidogen and phosphagen contain phosphoric acid, and since the other constituent of each appears in the urine, as we have just seen, it is not unexpected to find increased amounts of phosphoric acid excreted as a consequence of exercise. It is stated, further, that administering acid sodium phosphate by the mouth facilitates hard work. Uric acid (as urates) appears in the urine as a breakdown product of the nucleic acid coming from the nuclei of the cells of meat. An increased excretion results if any of the cells of the body themselves suffer destruction, as may happen in severe exertion. Potassium salts may be excreted under similar conditions.

ADDITIONAL HEAT PRODUCTION.—It is common knowledge that we get hot when we work. Temperatures of 104° F. to 105° F. are not uncommon, *i.e.* 6° F. above the normal. We also know that heat is produced by muscles as a result of contraction. Hill and his co-workers have shown this to consist of two parts: initial heat which just precedes the contraction, and delayed heat which follows later. It would therefore be expected that the blood leaving active muscles would be hotter than that going to them, and observation proves that this is so. There is also a definite heat production during glandular activity. The blood leaving the liver is about 1° F. hotter than that going to it.

TISSUE STORES OF FOOD.—It has long been known that both heart and skeletal muscles have considerable stores of carbohydrate in the form of glycogen. It is also known that both store carbohydrate as hexose phosphate (lactacidogen). These stores are depleted in skeletal muscle as the result of exercise following a period of starvation. In the heart they are depleted if it is perfused for some time with Ringer's fluid, which contains no glucose. These stores are doubtless made temporary use of during normal exercise, but as a rule they are rapidly restored from the carbohydrate of food or the glycogen stored in the liver.

NEGLIGIBLE OXYGEN STORAGE.—Muscles have been tested by many observers for the presence of stored oxygen. Verzar found that the oxygen tension in resting muscle is usually very low. This has been confirmed by other observers. But even if the tension were the same as arterial blood it would not

suffice for more than a few seconds' work. The same statement appears to be true of the other tissues, *e.g.* the brain.

TISSUE STORES OF BREAKDOWN PRODUCTS AND CARBON DIOXIDE.—That the muscles store for a time, at all events, the breakdown products that result from their metabolism is shown by three facts: (1) that the lactic acid concentration in the muscles is greater than that in the blood during activity; (2) that the H ion concentration in the muscles increases, sodium bicarbonate being changed to sodium lactate, the CO_2 being passed into the blood; (3) that metabolites continue to pass into the blood and to be excreted from it for a time after the exercise is over. The retention of CO_2 by the tissues must be negligible. So far as we know the whole of the CO_2 produced passes rapidly into the blood-stream.

SECTION II

CIRCULATORY CHANGES.—It is found that almost immediately exercise starts, two exchanges between tissue and blood must begin to take place: (1) the acquisition of oxygen; and (2) the discharge of CO_2 . If the exercise be hard and prolonged, we should find later that lactic acid was diffusing into the blood. That this is important will be readily seen from the fact that, if the muscles become so acid that they contain about 0.3 per cent. lactic acid, they can no longer contract; they have reached the lactic acid maximum. The diffusion of lactic acid into the blood puts off the time of cessation of work. It also stimulates the respiratory centre.

INCREASED BLOOD-FLOW TO TISSUES.—The absorption of O_2 and the passage of CO_2 from tissues to blood would be clearly aided by an increased flow of blood through the tissue concerned. Such an increased flow does in fact occur. Krogh counted the number of blood-containing capillaries in resting and active muscle. He found the number to be increased from 40 to 100 times. The capillary surface he found to be increased over 100 times. The actual flow of blood through the active muscles is increased from 10 to 20 times. Both these changes, the increased flow and the increased number of effective capillaries, are brought about by the local chemical effect, principally of metabolites, *e.g.* CO_2 , on the capillaries, and by the decrease in tone of the arterioles which supply them. The flow is further aided by the pumping action of the contracting muscles themselves,

the fact being remembered that the veins in between the muscle-strands have valves which cause the blood to flow towards the heart when these veins are compressed.

CHANGES IN BLOOD-PRESSURE AND HEART OUTPUT.—

The rise of blood-pressure is not large. At most it may be 180 to 200 mm. Hg, or about 80 mm. above the normal. On the contrary, the volume of blood flowing through the heart per minute may be increased three- or four-fold. In an extreme case it may change from 5500 c.c. per minute at rest to 35,000 c.c. per minute in strenuous exertion. The fact that the blood-pressure shows no corresponding change, proves that the resistance of the peripheral part of the circulation is greatly reduced during exercise. The cause of this is the increased flow through the active muscles. The rise of blood-pressure which occurs aids the rate of flow through the coronary and cerebral vessels which have no vaso-constrictor mechanism. The changes in the heart output with moderate amounts of work are brought about by increased stroke-volume, the rate remaining the same. In severe work with raised temperature, however, the rate may increase from 65 to 120–140 beats per minute.

THE INCREASED OUTPUT OF THE HEART.—The causes of this are: (1) the more than doubled heart-rate, *e.g.* from 72 to 150 beats per minute; (2) the more than doubled stroke-volume, from 80 c.c. to 190 c.c. In extreme cases both may be increased by nearly three, which gives a nearly nine-fold increase in the heart output. This large increase is brought about (*a*) by nervous impulses from the cerebrum removing the stopping action of the vagus, and causing the sympathetic acceleration of the heart; (*b*) by the arrival of additional blood at the great veins of the heart, thus setting Bainbridge's reflex into operation; (*c*) by the greater filling of the auricles and ventricles, bringing into operation Starling's law of the heart; (*d*) by the rise of temperature; (*e*) by the increased H ion concentration of the blood brought about by either the increased production of CO₂ or the escape of lactic acid into the blood, or both.

OTHER CIRCULATORY CHANGES.—Other parts of the circulation, *e.g.* the viscera and sometimes the skin, suffer a diminution in blood-flow in spite of the raised blood-pressure. This is brought about by the increase in tone of the vaso-motor centre, which is probably due to three factors: (*a*) impulses from higher centres; (*b*) increased H ion concentration of the

blood ; (c) lack of O_2 . This increase of tone of the arterioles does not, of course, affect the active regions, but only those which are not participating. The vaso-constriction in the splanchnic region brings digestion to a standstill, and indigestion may follow active exercise performed too soon after a meal.

CHANGES IN THE BLOOD.—The following factors are affected : (a) H ion concentration ; (b) temperature ; (c) oxygen content ; (d) CO_2 content. The P_H of the blood, instead of being the normal 7.4, falls even to 7.2. This is not so much because of the CO_2 produced by the active organs, but of the lactic acid. The latter diffusing into the blood displaces the CO_2 from the sodium bicarbonate, forming sodium lactate instead. The rise of temperature, as we have said above, may be as much as $6^\circ F.$, *i.e.* to over $104.5^\circ F.$ The oxygen content of the mixed venous blood leaving the tissues may fall as low as 4 per cent. (instead of being, as it frequently is at rest, 14 per cent.). This means that nearly three times as much oxygen has been taken up by the tissues during activity as during rest. This is called increased oxygen utilisation. The CO_2 content of the blood is also increased, but probably not to any great extent, because so much of the sodium bicarbonate has been replaced by sodium lactate.

HOW GASEOUS EXCHANGES ARE INCREASED.—If the dissociation curves of blood be examined (see Fig. 80, p. 180) it will be seen that increased acidity causes the unloading of rather more oxygen, particularly at lower oxygen pressures. The same effect is produced by a rise of temperature. Both conditions tend to assist the tissues to obtain the oxygen they require. An important further fact is the slowing of the blood through the dilated capillaries. This gives greater time for the equilibrium values to be approached. Two further factors may assist : first, the increased volume of the circulating blood caused by the emptying of the spleen, and, second, the greater richness in red blood-corpuscles which the blood suffers as the result of that emptying.

EFFECTS ON RESPIRATORY CENTRE.—The increased respiration rate, which is so marked a feature of exertion, is brought about by at least three factors : (a) by impulses from higher centres ; (b) by the increased acidity of the circulating blood ; (c) by the decrease in the oxygen content of the blood. There is a marked increase both in rate, which may be increased from, say, 18 to 36 per minute, and in depth, which may be increased as much as six times.

LUNGS.	At Rest.	Moderate Work.	Severe Exercise.
R = Respirations per minute .	16	20	30
D = Depth in c.c.	370	730	2130
V = Ventilation per minute in litres = $R \times D$	6	14.6	64
O ₂ = Oxygen intake per minute in litres = $V \times 5$ per cent.	0.3	0.73	4.1
CO ₂ = Carbon dioxide output per minute in litres	0.27	0.70	4.1
R.Q. = Respiratory Quotient (CO ₂ ÷ O ₂)	0.9	0.96	1.0
C = Carbon dioxide per cent. in alveolar air	5.7	6.2	6.6

BLOOD.

	At Rest.	Moderate Work.	Severe Exercise.
O ₂ per cent. arterial blood	19	18·5	17
O ₂ per cent. venous blood	14	12·5	6
Oxygen saturation of hæmoglobin in arterial blood	95	92	85
Oxygen saturation of hæmoglobin in venous blood	70	63	30
CO ₂ per cent. arterial blood	54	55	56
CO ₂ per cent. venous blood	58·5	60	67
P _H of arterial blood	7·4	7·35	7·2

HEART.

P = Pulse rate per minute	70	75	160
S = Stroke volume	86	162	233
M = Minute volume (P × S) in litres	6	12·2	37
B = Blood pressure in mm. Hg	110	140	190

METABOLISM.

Oxygen intake per minute in litres (see above)	0·30	0·73	4·1
C = Cals. per litre of O ₂	4·924	5·000	5·049
Cals. per minute (C × O ₂)	1·477	3·65	20·50

EVIDENCE OF RESPIRATORY QUOTIENT.—The facts with regard to the respiratory quotient have already been indicated. At the beginning of active exercise the amount of CO₂ excreted may be out of proportion with the amount of O₂ absorbed; in consequence the CO₂ to O₂ ratio may go above 1·5. There are two reasons for this: (1) That the higher centres, in anticipation of the work at hand, send impulses down to the respiratory centre, causing it to begin to carry out the rate and depth of respiration which, at that early period, is out of all proportion to the needs of the moment. In consequence CO₂ passes from the blood into the air in the lungs, there being no accompanying absorption of O₂ because the O₂ consumption has hardly begun. (2) That the muscles already engaged in activity demanding more than the available O₂ supply, begin to excrete lactic acid into the blood. This lactic acid tends to combine with the sodium bicarbonate of the blood to form sodium lactate, there being a corresponding liberation of CO₂, which is then excreted by the lungs. These two factors, one operating before the activity has really begun, and the other operating somewhat

later, produce the respiratory quotients greater than 1 which are sometimes met with. When once the individual has settled down to steady work, the respiratory quotient tends to remain fixed at or near 1, and since this is the respiratory quotient for carbohydrate (that of fat being 0.7 and that of protein 0.9), it follows that carbohydrate is the source of material from which the muscles are deriving their energy. When severe muscular exercise is complete, the respiratory quotient frequently falls to a low figure. The reason is that the CO_2 produced by the exercise has been eliminated by the lungs, and in consequence of O_2 being available and the muscles being at rest, the lactic acid, which has accumulated in the muscles and in the blood, and is in combination partly with the sodium and partly with the proteins, is now being resynthesised once more into the hexose phosphate (lactacidogen). In consequence the sodium of the blood requires CO_2 in order that it may reform the sodium bicarbonate once more. Large quantities of CO_2 are thus required, and the amounts excreted consequently fall to a low value, while the amount of O_2 absorbed remains at its usual resting value. Hence the respiratory quotient falls to a low value. Values of 0.3 are not uncommon.

EXCRETION DURING AND AFTER EXERCISE.—Under excretory products we must include CO_2 , which has been considered above, and those breakdown products which have already been described as appearing in the urine following exercise, namely, lactic acid, derived from the hexose phosphate (lactacidogen) of the muscle, creatinine, phosphates from the combined phosphoric acid, uric acid and potassium as the result of tissue breakdown (if any). In addition, we should refer to the water, salts, etc., secreted in the sweat.

TEMPERATURE REGULATION DURING EXERCISE.—We have already seen that when the muscles are actively engaged in producing external work, only a part of the heat which is liberated as a result of the chemical changes occurring, appears in the external work which they perform. At best not more than 38 to 39 per cent. of the total energy liberated appears as work. The remaining 60 per cent. appears in the form of heat. The same statement is true of the intact man. At rest, man may evolve 2400 calories. When performing 546 calories of external work the heat evolved may rise to 4575 calories, that is, there must be an increased heat loss of 1629 calories. This additional heat is dissipated in the following ways:—

(a) By warming the air in contact with the skin. This method

of loss will be favoured by a moist skin, since the minute air channels become obliterated, which prevent the external surface from becoming as hot as layers underneath. It is also favoured if a considerable skin surface be exposed to the air, and if that air be in motion relative to the skin surface, *e.g.* if the man is running against the wind.

(b) By increased loss of the heat via the lungs. Additional cold, more or less dry air is taken in and warm moist air given out with each breath. The quantity of heat lost in this way probably does not amount to very much.

(c) By the evaporation of moisture at the surface of the body. This factor is probably the most important one. With every c.c. of moisture evaporated, the man gets rid of nearly 540 small calories. These various factors have already been considered in some detail when describing the heat-regulating mechanism. This increased production of sweat is necessarily accompanied by a vaso-dilatation of some of the skin vessels, which will mean that the vaso-motor centre no longer keeps the skin vessels contracted as it was doing at first.

REPAYMENT OF DEBTS.—The O_2 debt is defined as the difference between the amount of O_2 taken in during the period of rest following exercise and a precisely similar period of rest that has not followed activity. Suppose, for the sake of argument, a man's resting consumption of O_2 is 250 c.c. per minute, while during exercise it goes up to 1250 c.c. When the exercise has been completed and the man comes back to the resting condition, the O_2 consumption during the first minute may be 1050 c.c., during the next minute 750 c.c., during the third minute 450 c.c., during the fourth 370 c.c., and during the next one after that, 280 c.c., and only after many more minutes will it have returned to the initial value of 250 c.c. per minute. The O_2 debt is the difference between the total amount of O_2 taken in if the consumption during all these minutes is added together and has subtracted from it the consumption which would have taken place during the same number of minutes at the rate of 250 c.c. per minute. In the above example the total for the ten minutes following exercise is 4205 c.c. During ten minutes' rest it would have amounted to 2500 c.c. The difference therefore is 1705 c.c., which is the amount of the O_2 debt. Now the O_2 debt is largely, if not entirely, due to the amount of lactic acid which has accumulated in the blood and muscles as the result of insufficient O_2 . When the period of activity is over and surplus O_2 again becomes available, the greater part of this lactic acid is reconverted by the muscle-tissue into the hexose phosphate

complex and glycogen from which it originally started. This reconversion absorbs O_2 . It is not difficult to calculate the relationship between the amount of O_2 utilised and the lactic acid complex built back again. Approximately 1 litre of O_2 is equivalent to 6 grammes of lactic acid, as the following values obtained by Hill show :—

	O_2 Debt. Litres.	HL Accumulation Grammes.
i. Running 225 yards on the flat in 23·4 seconds	8	48
ii. $\frac{1}{4}$ -mile race, followed by violent gymnastics for 30 seconds, leading to complete ex- haustion	13	78
iii. "Standing-running" all out for $3\frac{1}{2}$ minutes, breathing 50 per cent. O_2	15-18	90-108

From a knowledge of the O_2 debt it is therefore possible for us to calculate what quantity of lactic acid is built back again into a complex on completion of the exercise. If now we know the total work that was performed, and the heat which was produced during that work, we can ascertain the total amount of lactic acid complex broken down, and we can therefore show what percentage of this remained in the circulation at the end of the exercise. We should expect the debt to reach its highest as a result of the most strenuous exercise. Experiment confirms this.

SECTION III

TRAINING.—In the training of an athlete three factors at least are of importance. (1) There is a marked increase in the weight and efficiency not only of the actual muscles which are called on to perform the particular kind of work required, but also in accessory muscles, the most important being those of the heart and respiration. The heart undergoes hypertrophy, its output per beat increases, the variation in the output per beat increases also, and, as a rule, the rate of its beat per minute is not only slower during the performance of the exercise in the trained man than it would be in the untrained man, but it is also slower while the individual is at rest. Thus, an untrained man with a normal pulse rate of 73 at rest, may, after training, have a resting pulse-rate of 58. The same individual when performing work when untrained may have a pulse-rate of 160, while after training and then performing the same amount of work the pulse may be

only 115. The return of the heart-rate to its resting value after the period of activity is over is also more rapid in the trained than in the untrained. (See later.) The increased weight of the muscles causes the protein content of the body to increase, this being provided for during training by the administration of a rich protein diet. (2) Certain parts of the body, notably the fat depots, decrease in weight, and it is said that losses also occur in muscles which are not used during the training. The body thus gradually converts itself into a machine which will develop the greatest possible output of power, and will have the smallest possible superfluous load to which that power is applied. (3) Quite as important as these physical changes are the mental ones effected by training. By trial over a series of days the brain learns how to control the muscles with the greatest efficiency. This does not only consist of the correct co-operation of muscle with muscle so as to perform most efficiently a particular movement, but in addition, it is concerned with the velocity to be given to these movements as a whole. The following example will make my point clear. A runner wishes to complete a mile in the shortest possible time. If he lets himself go at first and runs at his utmost speed and continues to do so, measurement will show that his speed rapidly falls off, so that the last quarter-mile is performed at a speed far below that of the first quarter. On the contrary, supposing that he starts at a slow speed, he may find that even the fastest speed of which he is capable during the last quarter-mile lap does not really tax his capabilities to the utmost. It is only after doing the mile a number of times that the man learns by trial the pace he should set in order just to complete the distance when his endurance is becoming exhausted. Not only is such precise knowledge of the greatest importance to individual athletes, but it is equally important when one man is controlling the energy output of a number of others, *e.g.* the stroke in an eight. These are probably only two aspects of the mental factors of training, but they suffice to emphasise the importance of this side of athletics.

SECOND WIND.—It is not clear at the present time what is the cause of this well-known phenomenon, which occurs in both trained and untrained individuals. Probably, however, the following explanation will make clear one or two of its aspects. It has been shown in the section on the respiratory quotient that during the early stages of severe exercise the quantity of CO_2 excreted is in excess (sometimes greatly in excess) of the O_2 which is being taken in. The reason for this CO_2 excess is that lactic acid is passing from the muscles into the blood, is combining

with the sodium bicarbonate to form sodium lactate, and the CO_2 in consequence is passing into the blood to be excreted by the lungs. This CO_2 is additional to that produced by the oxidation of the carbon in the tissues, and therefore the amount of CO_2 to be excreted is greatly above the amounts normally found. Hence the respiratory centre is powerfully stimulated and the feelings of anxiety which are experienced during the early stages of severe muscular effort are probably due to the presence of this excess CO_2 in the blood. During the continuance of the muscular work, however, the respiratory quotient falls from the high value which it has temporarily held to remain for the rest of the period of exertion at approximately the value of 1. This fall of the respiratory quotient may be gradual or sudden and may very likely be associated with the gradual or sudden appearance of what is called second wind.

THE RETURN TO THE RESTING STATE.—Curiously enough, the differences between a trained and untrained man are just as clearly shown by the physiological changes which occur on the termination of the period of exercise as are those which are shown during the period of exertion. For example, in the table below (Pembrey) is given the number of heart-beats which occur in fifteen seconds in a trained and an untrained man immediately after a short period of exertion, which consisted of running up and down stairs, and occupied thirty seconds.

	Trained Man.		Untrained Man.	
	Immediately after exercise.	5 minutes later.	Immediately after exercise.	5 minutes later.
Heart-beats per $\frac{1}{4}$ minute	33	15	38	24

The heart-beats after a long period of rest were 16 and 17 respectively. It will be observed that in the trained individual the number of beats five minutes after the exercise was normal, whereas in the untrained man it was still well above the normal, thus indicating that the untrained man has to make good a bigger debt than does the trained. This is because his circulatory system and the other important functions of his body have not been able to increase their output to the same extent as have those of the trained individual, and in consequence the circulatory system and the other organs have to continue working at an enhanced speed for a longer time when the exercise is at an end than have those in the trained man.

CHAPTER X

THE CENTRAL NERVOUS SYSTEM

SECTION I

INTRODUCTION.—The central nervous system consists essentially of three parts: A, the cerebrum (cerebral hemispheres), B, the cerebellum, and C, mid-brain, medulla, and spinal cord, which together form one main connective system. Structurally they are composed of nerve-cells, nerve-fibres, and neuroglia. The nerve-cells are usually collected in groups. On section these have a grey colour and are referred to as “grey matter.” The medullated axons of these cells are also usually collected into groups, causing the parts of the central nervous system which they occupy to be called “white matter.” In the spinal cord the white matter lies on the outer side, whereas in the cerebellum and cerebrum it is the grey matter which forms the outer layers.

The functions of these parts may be ascertained (*a*) by removal of a part under an anæsthetic and an investigation of subsequent behaviour, or (*b*) by the electrical stimulation of a part under an anæsthetic, and the investigation of behaviour. These two methods have been applied to men and to animals. Great care should, however, be taken in interpreting animal behaviour and applying it without alteration to man. Man's brain is much more highly organised and in many ways physiologically different from that of lower mammals. Briefly, it is the function of the cerebrum (*a*) to receive visual, auditory, and tactile sensations, (*b*) to correlate these in a suitable manner, (*c*) to store up a record of these sensations, (*d*) to initiate suitable movements, and (*e*) to control the behaviour of the animal as a whole. The cerebrum is found to be a crossed structure: that is to say, sensations from the right-hand side of the body arrive at the left-hand half of the cerebral cortex, whereas impulses required to set in operation movements on the left-hand side of the body start on the right-hand side. Not only is the cerebrum “crossed,” but it

is also "inverted"; that is, nerve paths connected with the lower half of the body terminate at its upper part. Movements of the upper part of the body are initiated by impulses from the lower part of the cerebral motor cortex. This is not true however of the cerebellum, which is neither "crossed" nor "inverted"; that is to say, the right-hand half deals with the right-hand half of the body, and the part devoted to the arms is on the upper surface. It is the function of the cerebellum to carry out complicated interactions which affect many muscle groups, for example those which are concerned with the preservation of balance. The function of the mid-brain, medulla, and cord is partly to act as conductors for the cerebrum and cerebellum, and partly to act as autonomic centres for such functions as respiration, heart control, etc. Details of these will be given in the sections which follow. The paths taken by the different axons in the central nervous system may be mapped out by three principal methods: (1) By studying the order in which the fibres obtain their medullary sheaths during embryological development. (See Fig. 97.) Generally speaking,



FIG. 97.—Section through the cervical spinal cord of a new-born child, stained by Weigert's method to show absence of medullation in pyramidal tract. (Bechterew.) (From Starling's *Principles of Physiology*.)

ca, anterior commissure; Fp, crosses pyramidal tract; Fe, direct cerebellar tract; rp', posterior root-fibres.

the longer fibres become myelinated later than do shorter ones. Thus the pyramidal tracts do not in man acquire their sheaths until after birth. (2) By cutting groups of fibres, allowing them to degenerate, and subsequently ascertaining which direction the degenerated fibres have taken by following them through a series of sections. It should be noticed that only the severed axons degenerate; the part still connected with the nerve-cell does not do so. (3) By applying nicotine. This drug paralyses synapses between nerve-cells. If, therefore, the nerve-fibres under investigation are found to be paralysed after applying this drug to a ganglion, this shows that the nerve has relayed there with a fresh axon. This method is of particular value in tracing out the more peripheral parts of

the central nervous system, e.g. the sympathetic ganglia and nerve-fibres.

When these paths have thus been traced, it is found that

they may be placed in one of four categories: (a) paths connecting sensory end-organs with effector organs such as muscles or glands—local “reflex arcs”; (b) paths connecting sensory end-organs with the central nervous system—“sensory tracts”; (c) paths connecting the central nervous system with effector organs—“motor tracts”; and (d) paths connecting one part of the central nervous system with another part—“association or correlation tracts.” Now it appears to be a rule in the case of all four categories that there shall be three nerve-cells with their axons interposed. These are referred to as the first, second, and third order relays. Thus, axon number one may convey the impulse from the end-organ into the spinal cord; here it forms dendritic connections with the nerve-cell of relay number two; the axon of this nerve-cell conveys the impulse to an anterior horn-cell which belongs to relay number three. The axon of this cell runs to the muscle or gland, setting it in operation.

This rule is frequently of assistance for remembering where a particular nerve-path relays on its course to its destination. Another rule which is of assistance is that if a crossing of the impulses from one side of the central nervous system to the other side has to be carried out, it is almost always second order relay-fibres which do this. Many examples will occur in the sections which follow, illustrating these two rules.

SECTION II

INTELLECT.—It is obviously not to size, weight, or strength that man owes his dominion over other creatures, but to manual dexterity and intellect. The former placed the monkey in a position superior to that of the other mammals. It is the latter that has made man supreme over them all. Intellect in its material aspects may be considered under three headings: ideals, communications, and inventions. By ideals are meant laws, rules, and standards of correct behaviour. By communications are meant speech, the telephone, the gramophone, and wireless; also writing, printing, drawing, and the cinema. By inventions are meant new methods of communication—television; new methods of transport—the aeroplane; new methods of lighting and cooking, new treatments of disease.

In consequence of these possessions man can do more in his life than any other creature. He can profit by the experiences of his ancestors and contemporaries. He can become a surgeon or an engineer. All such activities display his intellect and this he owes to the great development of his cerebral hemispheres. The

old ideas of the phrenologists were right in principle. The cranium, they said, contains the parts to which intelligence and character are due. It was in details that they were wrong. This bump, they alleged, shows courage and that one love of sport. Even if the bumps on the outsides of our skulls did indicate the bumps on our cerebrums (which they do not) we should have no basis on which to found an opinion of a man's capabilities and outlook. The criminal and the criminologist, the house-builder and the house-breaker, could not be differentiated by measurements of their brains.

On the other hand there is ample evidence of the functions performed by many parts of our cerebral hemispheres, as we shall see later in this section. By this part we see ; by another we feel. Destroy this part and we are deaf, or that part and we are paralysed. But there are other parts : "the silent areas" of which we at present know little. Interfere with these and a man's character may be changed. The clever may become stupid, the friendly a homicide. The more highly developed a man's mind, the more readily do we detect in it the signs of injury and disease.

Experiments on animals show results quite different from those which accident and disease demonstrate in man. Complete loss of sensation and voluntary movement would follow the removal of man's cerebrum. In animals this is not so. Goltz removed the cerebral hemispheres of a dog under an anæsthetic. The animal lived for eighteen months afterwards. It walked about its cage. It slept at night. A bright light caused it to blink. A loud sound caused it to start. A pinch made it snarl. But it did not recognise food, which had to be placed by hand into its mouth. It showed neither pleasure nor fear. It did not recognise the man who fed it. In other respects it appeared to be a normal dog. Man under similar circumstances would be paralysed and anæsthetic. Great caution must be exercised when applying results of experiments on animals to man, particularly when they are on the central nervous system.

THE CEREBRUM.—The cerebral hemispheres in man form an ovoid mass exceeding in size all the rest of the central nervous system put together. They are separated into right and left halves by the great longitudinal fissure. On the outer side each hemisphere presents a deep cleft, the Sylvian fissure. The whole of its surface is thrown into folds called convolutions. The fissures between divide the brain into lobes. The chief ones are : the frontal, ascribed to voluntary movement ; the parietal, to which sensations of various kinds are distributed ; the calcarine,

for vision ; the temporal, for hearing ; and the limbic area, for taste and smell. (See Fig. 98.)

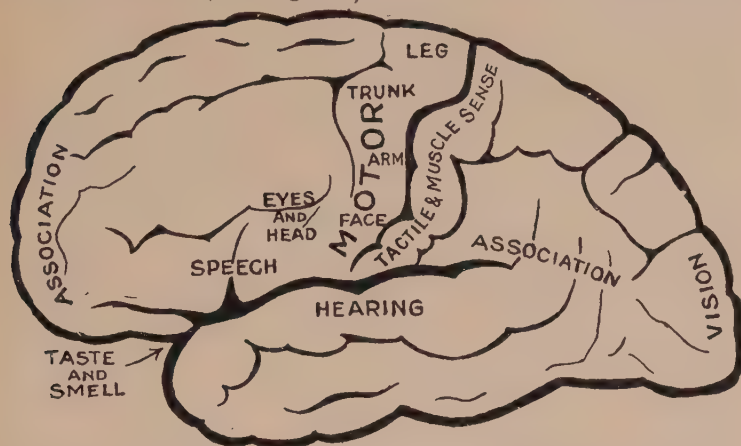


FIG. 98.—Diagram showing localisation of function in the cortex of the left cerebral hemisphere.

HISTOLOGICAL STRUCTURE.—On transverse section the cortex is found to consist of an outer layer of grey matter covering

	Layers.	Cells.	Fibres.
1	Plexiform layer .	Horizontal cells of Cajal	Tangential fibre layer.
2	Small pyramid cell layer.	Small pyramid cells . Small granule and double brush cells.	Outer radial fibre layer.
3	Outer medium pyramid cell layer.	Medium pyramid cells . Small granule and double brush cells.	Outer radial fibre layer
4	Outer large pyramid cell layer.	Large pyramid cells .	Outer layer of tangential white fibres. Outer line of Baillarger.
5	Stellate cell layer .	Small stellate cells. .	Middle radial fibre layer.
6	Inner large pyramid cell layer.	Large pyramid cells (Betz cells occur here in motor cortex)	Inner line of tangential white fibres. Inner line of Baillarger.
7	Inner medium pyramid cell layer.	Medium pyramid cells .	Inner radial fibre layer.
8	Fusiform cell layer	Fusiform cells (specially marked in claustrum).	Inner radial fibre layer.

Internal to the fusiform cell layer 8, lies the white matter of the cerebral cortex.

a central mass of white, medullated fibres. On microscopic examination eight layers will be identifiable in the grey matter. (See Fig. 99.)

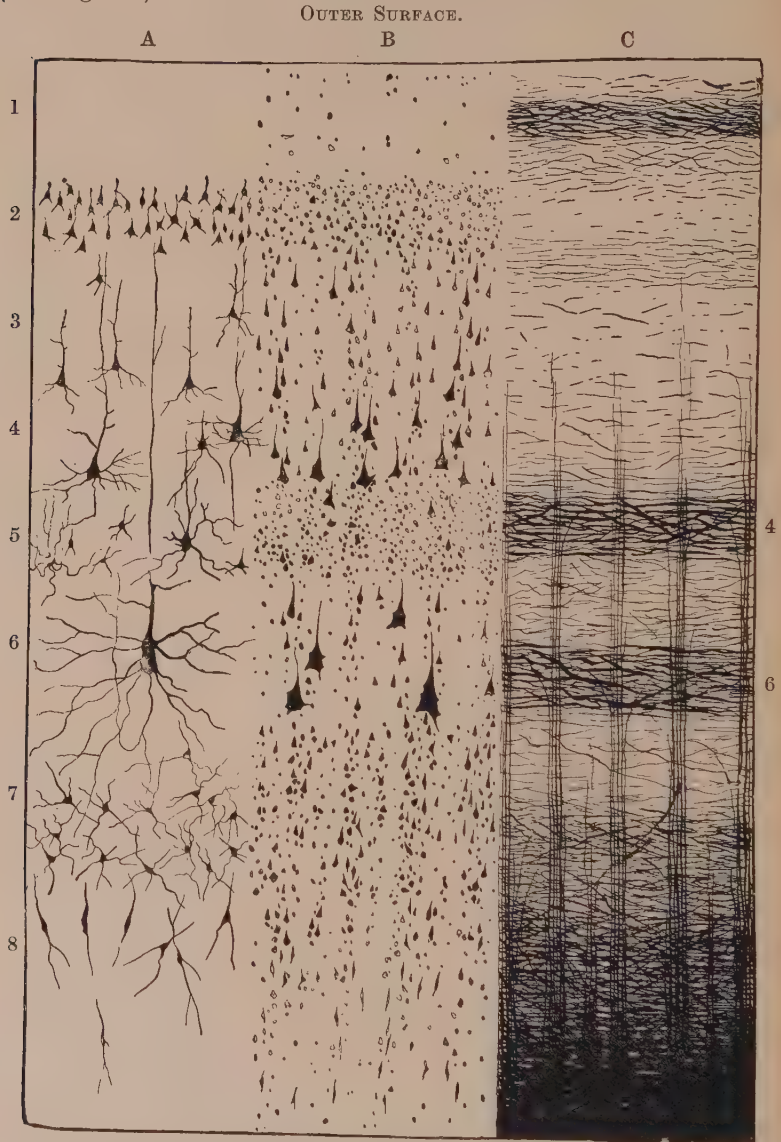


FIG. 99.—Diagram to show the layers of cells and fibres in the grey matter of the cortex of the human cerebral hemisphere, stained by three different methods: A, Golgi; B, Nissl; C, Weigert. (From Luciani's *Physiology*. Macmillan & Co.)

The pyramidal layers of cells of all sizes give off three different kinds of fibre : an apical one running towards the outside, a basal one running towards the white matter, and transverse ones which run tangentially. The tangential fibres in group 1 are largely composed of the apical fibres which have reached the outside surface and then have turned at a right angle to ramify with other similar cells. The tangential outer and inner lines of Baillarger are formed of the horizontal fibres of the giant pyramidal cells. The radial layers, on the other hand, are formed by the apical or basal fibres of all the different cells which are present throughout the section.

About 60 per cent. of the whole area of the cortex shows all these layers when fully developed. The calcarine area becomes more elaborate, the voluntary motor area becomes somewhat simplified, while the olfactory and gustatory area is very greatly simplified.

THE THREE MAIN TRACTS OF FIBRES which run from the different parts of the cerebral cortex are : (1) Short association fibres running from one part of one side to a different part of the same side ; thus, one tract, the superior longitudinal fasciculus, runs between the frontal and occipital lobes. Others connect temporal and occipital lobes, frontal and temporal lobes, parietal and occipital, etc. (2) Commissural fibres which connect the two corresponding halves of the cerebrum. These are grouped in the corpus callosum, which contains all fibres except those from the olfactory bulb and small parts of the temporal lobe. (3) The long path projection fibres, the objects of which are to connect the cerebral cortex with lower parts of the central nervous system ; thus the anterior part of the corona radiata of the internal capsule is formed (*a*) of fibres running from the frontal lobe to the cerebellum via the pons, and (*b*) of fibres which, ascending from lower parts of the central nervous system, have relayed at the optic thalamus. That is, both ascending and descending fibres are present.

The superior part of the corona radiata and middle part of the internal capsule contain (*a*) *fibres conveying sensations*, which, ascending from lower parts of the central nervous system, have relayed at the optic thalamus and are going to the post-central sensory area ; (*b*) *fibres for voluntary movement*, that, starting from the giant Betz cells in the praecentral motor area, are passing down as the pyramidal tract for voluntary movement. The posterior parts of the corona radiata and internal capsule are formed (*a*) of fibres which comprise the optic tracts and have relayed in the external geniculate body of the optic thalamus ; they convey

visual sensations to the calcarine cortex; (b) of fibres which travel to the retinae of the eyes from the calcarine region; (c) of fibres for synergic eye and limb muscle control, which run down to the pons and thus reach the cerebellum.

The inferior parts of the corona radiata and postero-external parts of the internal capsule are formed (a) of fibres which have relayed in the internal geniculate body and are conveying auditory sensations to the superior temporal convolution; (b) of fibres which, leaving the temporal lobes, pass down to the cerebellum, via the pons. The relative positions of the fibres as they pass through the internal capsule are shown in Fig. 100.

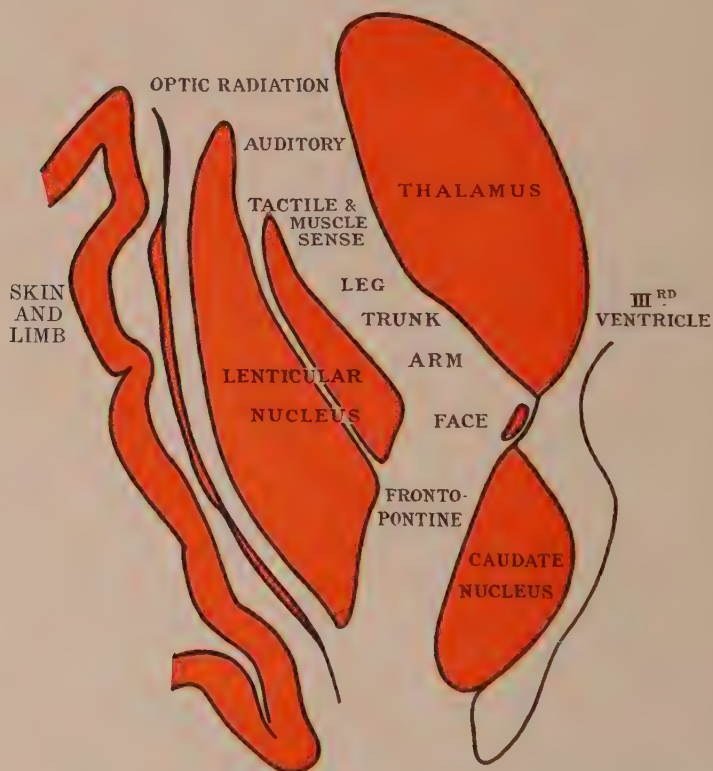


FIG. 100.—Diagrammatic representation of the right internal capsule, as seen in horizontal section.

Anatomically there is no demarcation between these sets of fibres. They form rather a continuous sheet of medullated axons, which, sweeping downward and inward from all parts of the cerebral cortex, converge to pass through the internal

capsule, and thus descend to the lower parts of the central nervous system.

BASAL GANGLIA.—The internal capsule is composed of medullated axons which have passed downwards and inwards through the corona radiata from all parts of the cerebral cortex, the right- and left-hand capsules making roughly a right angle with one another. The corpus callosum, on the other hand, runs horizontally from right to left. There are thus two conical areas lying between it and the two capsules. These are occupied partly by the lateral and third ventricles, which are filled with cerebro-spinal fluid, and partly by the optic thalamus and caudate nucleus. Below the capsule is another conical area which is occupied by the lenticular nucleus. (See Fig. 100.) This is part of the corpus striatum.

THE MID-BRAIN.—During the passage of the fibres through the corona radiata ascending and descending fibres have been intermingled. As they approach the internal capsule a separation takes place. The ascending fibres lie above, since they are emerging from the optic thalamus. Descending ones descend more steeply into the internal capsule. This separation into ascending and descending fibres, with local modifications, will be found to be retained throughout the lower portions of the central nervous system. The rule is that ascending fibres occupy a posterior, and descending fibres an anterior, position. In addition to these ascending and descending projection-fibres, we find in the mid-brain two pairs of elevations on its posterior surface, the superior corpora quadrigemina, which are relay stations for the eye muscles, and the inferior corpora quadrigemina, which are relay stations for fibres connected with hearing. We also find two important landmarks, the red nuclei and superior cerebellar peduncles. We shall see later that they form part of the rubro-spinal tract which connects the cerebellum with the muscles of the limbs for synergic control. In addition, important fibres from cerebellum to cerebrum pass up via the superior cerebellar peduncle.

THE CEREBELLUM.—On the anterior aspect of the brain stem we find, as we should expect, descending fibres, and posterior to them ascending ones. Encircling these we find structures which belong to the cerebellum. Behind are parts of the cerebellum itself. To the sides and in front run the fibres of the pons which connects right and left halves of the cerebellum. (See Fig. 101.)

The pons also forms part of the main pathway from cerebrum to cerebellum. (See page 267, Fig. 113.)

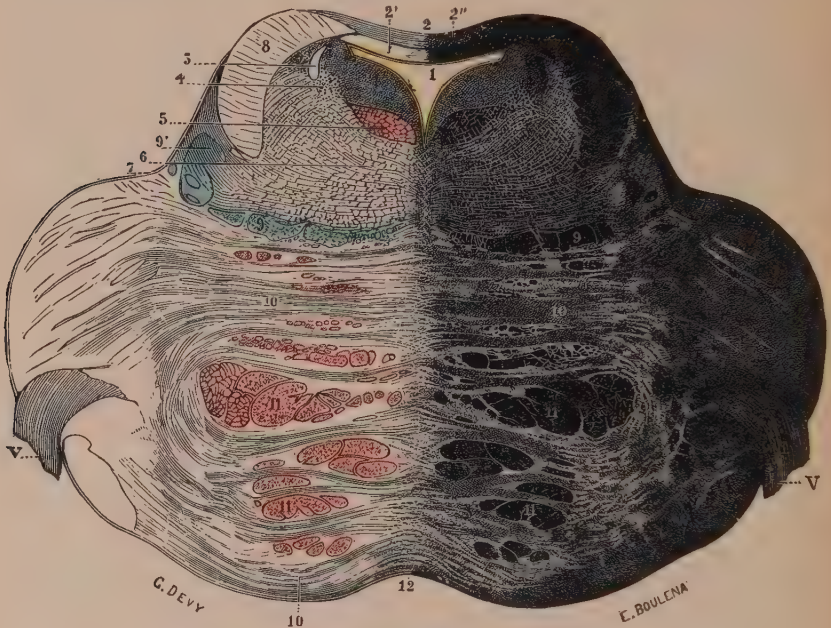


FIG. 101.—Coronal section of the pons, at its upper part. (Testut.)
(From Gray's *Anatomy*.)

1, fourth ventricle; 2, anterior medullary velum; 3, mesencephalic root of fifth nerve; 4, nerve-cells associated with this root; 5, posterior longitudinal bundle; 6, formatio reticularis; 7, lateral sulcus; 8, section of superior peduncle; 9, medial fillet; 9', lateral fillet; 10, 10, transverse fibres of pons; 11, 11, pyramid; 12, raphe; V, exit of fifth nerve.

THE MEDULLA.—In the upper part of the medulla we find an important landmark, the *sensory decussation*. Ascending sensory fibres which hitherto have not crossed do so here, thus joining those in the direct spino-thalamic tract which crossed lower down in the cord immediately they had entered. The tract thus formed is called the *lemniscus* or *fillet*. This forms the main ascending sensory pathway going to the optic thalamus and thence, after relaying, to the post-central sensory cortex. Lower down in the medulla occurs the *motor decussation*. Here, fibres which are descending in the pyramidal tracts cross with their neighbours and go to the opposite side. In this new situation they descend the cord, passing off as they go to their respective anterior horn-cells.

In addition to these main tracts and their decussations, we find nuclei of important cranial nerves in the medulla, which control the heart, circulatory system, and respiration. Each of these has been dealt with in detail in previous chapters.

DECEREBRATE RIGIDITY.—When the cerebral hemispheres are destroyed in man, there is increased tonicity and paralysis of the muscles. In animals this does not take place unless in addition the rubro-spinal tracts are destroyed. On the other hand, if the rubro-spinal tracts alone are destroyed no marked rigidity occurs. In other words, while in man the pyramidal tracts appear to have entire control, in the lower animals this control is divided between pyramidal tracts and rubro-spinal tracts. In both man and animals, however, it appears to be of such a nature that it holds in check tonic impulses originating elsewhere. In man, these appear to be principally from the spinal reflex centres. The cerebellum seems to play a minor part. This is shown by the fact that persons born without cerebellar hemispheres are hardly detectable from normal people. In animals, on the other hand, the part played by the cerebellum appears to be greater. This matter will be referred to again in Section XII of this chapter.

SECTION III

VISUAL SENSATIONS.—We shall see in Chapter XII that the retina consists essentially of three layers of cells: (a) light-sensitive rods and cones; (b) bipolar cells; and (c) ganglion cells. Now, since first, second, and third order neurones should be found on the course of any sensory nerve, they should also be found between the rods and cones and the calcarine cortex. This is found to be the case. The bipolar cell is the first order neurone, the ganglion cell the second order neurone, so that the optic nerve and tract consist of second order relay fibres. These travel to the external geniculate body and, having relayed there, third order relay fibres distribute the impulses to the calcarine cortex. Fig. 102 shows these fibres in further details. It will be seen that four separate bundles go from each eye, namely, right-hand half of peripheral retina, right-hand half of fovea, left-hand half of fovea, and left-hand half of peripheral retina. These travel to the chiasma, where they are redistributed in the following way: those from the right-hand peripheral retina and right-hand half of the fovea travel to the right-hand external geniculate body, and so reach the right calcarine cortex; the left-hand fibres go to the left-hand calcarine cortex in a similar manner.

DISTRIBUTION AT CALCARINE CORTEX.—Gordon Holmes describes the distribution of the fibres at the calcarine cortex as follows: Those from the foveæ occupy large areas at the most posterior extremity of the calcarine cortex. Next,

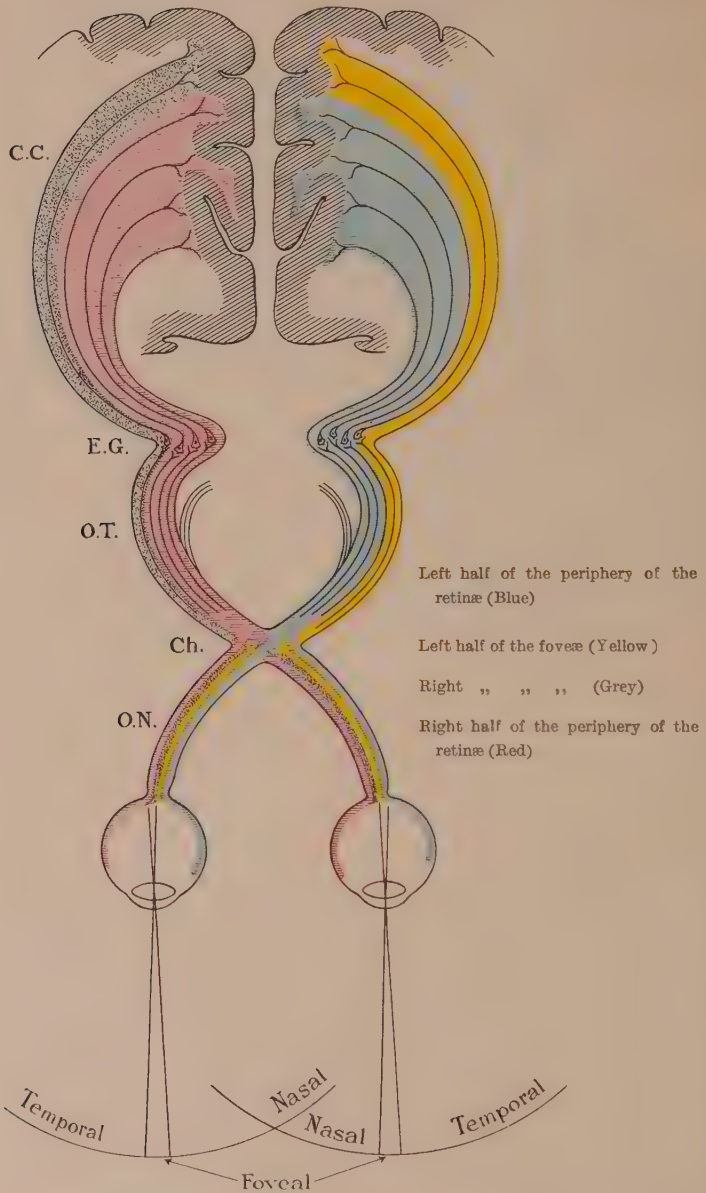


FIG. 102.—Diagram showing connections between the retina and the calcarine cortex.

O.N. = optic nerves; Ch. = chiasma; O.T. = optic tracts; E.G. = external geniculate body;
C.C. = calcarine cortex.

occupying a smaller area, come the more peripheral fibres ; more anterior still and occupying a smaller area still are those from the most peripheral parts of the retina. In each case fibres from the upper part of the retina are distributed to the upper part of the calcarine cortex, and *vice versa*. That is to say, images in the lower part of the visual field will, since they cross in the lens system of the eye, be distributed to the upper part of the calcarine cortex ; that is, the calcarine cortex itself is inverted. Since objects on the right travel to the left cortex, it is also "crossed," thus bringing it into line with those parts of the cerebral cortex which have to do with the limbs.

The fibres for the pupillo-motor reflex travel up the optic nerves and, without crossing in the chiasma, go to the anterior corpora quadrigemina to reach the part of the third nerve nucleus concerned with the innervation of the sphincter pupillæ muscle. Reference to Fig. 102, will show that section of one optic nerve will cause blindness in one eye. On the other hand, section of one optic tract will cause blindness of those halves of both retinæ which are on the same side as the tract. Injury of the middle of the chiasma, such as may occur in tumours of the pituitary body, will affect the nasal halves of both retinæ and produce double temporal blindness.

The control of eye movements is an important factor in the efficiency of vision. It is necessary that the visual axis should be directed with speed and precision. There are movements which the eyes perform together, turning to right, to left, up, or down. But there are also movements in which the eyes rotate in opposite directions, causing "convergence" or "divergence." These movements may be brought about voluntarily and involuntarily. The six muscles which cause them will be described in the section on eye movements in Chapter XII.

VOLUNTARY EYE MOVEMENTS are carried out by impulses which originate in the Betz giant pyramidal cells of the anterior inferior part of the voluntary motor precentral (Rolandic) cortex. The axons from these cells pass downwards and inwards in the corona radiata to reach the genu or angle of the internal capsule. The fibres now descend vertically till they reach the level of the superior corpora quadrigemina (colliculi), where they cross over to the other side and pass to the third, fourth, and sixth nerve nuclei. This crossing of the fibres on their way down causes the cortex on the right-hand side to innervate the left side nerve centres, and *vice versa*. The right eye will thus be turned towards the left by impulses which originate on the right-hand side of the brain. These have crossed to the third nerve nucleus on the left-

hand side, which sends impulses to the internal rectus of the right eye. At the same time the impulses go to the sixth nerve nucleus on the left, and this innervates the left-hand external rectus muscle, thus causing the left eye also to turn to the left. It will be observed that just as the right-hand side of the cerebrum controls the left arm, so it controls the eyes when they make movements towards the left-hand side.

THE FIXATION REFLEX retains the gaze on external objects when they have been directed towards them. The reflex is carried out with extreme precision, and it develops at a very early age. Two sets of paths are involved, those from the retinae to the calcarine cortex, and those from the calcarine cortex either directly or after relaying in the superior corpora quadrigemina to the third, fourth, and sixth nerve nuclei, probably of the opposite side. The mode of action of this reflex may be explained as follows: Suppose the eyes to be directed voluntarily towards an electric lamp. The stimulus will fall partly on the right and partly on the left halves of the retinae. Both right and left calcarine cortices will therefore receive impulses, and from these cortical areas, impulses will pass to both right and left sets of nerve nuclei. No movement of the eyes will take place, since the impulses sent out by one set of nuclei will be opposed by those sent out by the other. Suppose, however, that the lamp be moved a little to the right. The images cast on the retinae will, since they are reversed, move slightly to the left, and thus the left-hand halves of the retinae will be more strongly stimulated. In consequence the left-hand calcarine cortex will receive impulses which are more powerful than those reaching the right, and the right-hand nerve nuclei will more powerfully contract the muscles they control; that is to say, the turning of the eyes towards the right will be increased, thus causing the eyes to follow the movement of the lamp. Ordinarily we can turn this reflex on or off at will. Very rarely, control becomes defective, and then it is only with a great effort that the gaze can be turned away from an object on which it is fixed.

THE CORRELATION OF HEAD AND EYE MOVEMENTS is of two kinds: compensatory when we wish to rotate the head and still preserve the gaze on some stationary object, and associative when we wish head and eyes to rotate in the same direction so as to follow an object which is moving past us. Both these movements appear to be controlled by the inferior olivary bodies.

For the protection of the eyes an important reflex is provided which can be set in motion by vision and hearing, or even by smell

and taste. This reflex causes firm closing of the lids, raising of the arm in front of the eyes, the flexing of the neck and spine, and even the raising of the knees. This reflex operates through the tecto-spinal tract, which, commencing in cells in the superior corpora quadrigemina, descends near the posterior aspect of the mid-brain. The fibres cross to take up a more anterior position and end near the anterior horn-cells.

SECTION IV

AUDITORY SENSATIONS.—It will be shown in Chapter XIII that the cochlea consists essentially of a mechanism for turning sounds into nerve stimuli. The fibres of the auditory nerve which ramify among the hair-cells of the cochlea are first order neurones, and their cell-bodies are found in the spiral ganglion of the cochlea. This is the counterpart of the posterior root ganglion of the spinal nerves. The axons which leave these cells are the auditory portion of the eighth cranial nerve. As we shall see in a later section, the vestibular portion of this nerve is concerned with the poise of the head. Having entered the C.N.S. at the lower border of the pons, the nerve divides into two parts. The larger portion relays in the lateral principal nucleus (the tuber acoustica) which lies behind the inferior cerebellar peduncle, while the smaller portion relays in the anterior accessory nucleus the trapezoidal nucleus. (See Fig. 103.) This lies in front of the

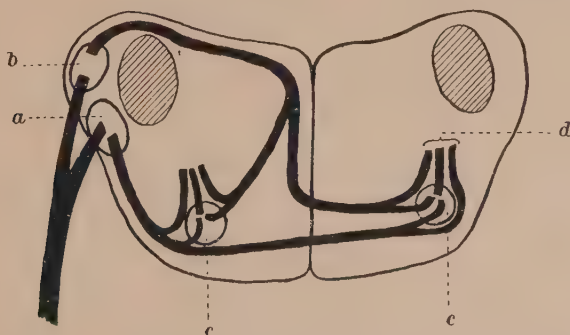


FIG. 103.—Diagram showing the path for auditory impulses in the pons.

a, accessory nucleus; *b*, tuberculum acusticum; *c*, trapezoid nucleus; *d*, lateral fillet.

inferior cerebellar peduncle. From these nuclei second order relay fibres cross to the opposite side and form the lateral part of the fillet, the main ascending sensory pathway. Those from the principal nucleus travel near the floor of the fourth ventricle

and then turn forwards, passing across to the opposite lateral fillet. Those from the accessory nucleus cross those coming from the opposite side, thus forming the trapezium. These also enter the lateral fillet. The second order relay fibres now ascend the fillet; the majority end at cells in the internal geniculate body. Here they relay, and third order fibres convey the sensations to the superior part of the temporal cortex. A few, however, go to the inferior corpora quadrigemina and a few to the superior olives. The objects of these connections will be considered shortly.

THE TEMPORAL CORTEX is divided physiologically into two parts: the audito-sensory area directly connected with the eighth nerve by the path described above, and the audito-psychic area which lies just underneath. In the audito-sensory area, which is largely hidden in the Sylvian fissure, the auditory stimuli are interpreted as sensations of tone varying in pitch, loudness, and quality. Histologically it may be identified from the richness of all its layers in cells and fibres. Sections stained to show nerve-fibres exhibit a band running parallel to the external surface, the line of Kaes.

The audito-psychic area which occupies the lower two temporal convolutions has only small cells, and no typical line, is associated with the interpretation of sounds, their localisation, and their association with the objects which made them.

Three reflexes must now be briefly mentioned: (1) The auditory reflex which causes contraction of the tensor tympani muscle when sounds fall on the ear. (2) The auditory protective reflex which, as the result of a sudden noise, causes blinking of the eyes. This may, if the sound is very loud indeed, produce, in addition, the holding of the breath and loss of tone in the limbs, thus causing the body to fall in a heap. The details of the reflex are not known. They may travel via the superior olives to the tenth cranial nerve for holding the breath, and to the red nucleus or Deiters' nucleus for cessation of movement. The mechanism is obviously protective to guard the eyes, the respiratory passages, and the body generally, from injury. (3) The auditory eye-turning reflex which probably travels via superior olives or inferior corpora quadrigemina and causes the eyes to turn towards a sound.

SECTION V

SENSATIONS OF LIMB POSTURE AND MOVEMENT.—

These sensations are called proprioceptive by Sherrington. Some other physiologists call them kinæsthetic sensations, since they

inform the central nervous system of the positions which the limbs occupy, or the movements which they are carrying out. Experiment shows that they are necessary during voluntary movements to give information whether the force applied by the muscle has been sufficient in intensity and duration to carry out the required act. It is found, further, that similar information is necessary for the correct correlation of the different muscle-groups which move a limb and which move different limbs in the performance of such an act as walking. Lastly, they are wanted for the correct estimate of the resistance against which the muscles are operating, *e.g.* for the appreciation of a weight held in the hand.

The sensory end-organs concerned differ greatly in their histological details. Pacinian corpuscles and muscle-spindles are some of the best known. They are found in the periosteum of bone, in tendons, cartilage, muscles, and in subcutaneous tissues. Pacinian corpuscles probably record pressure and may therefore be used

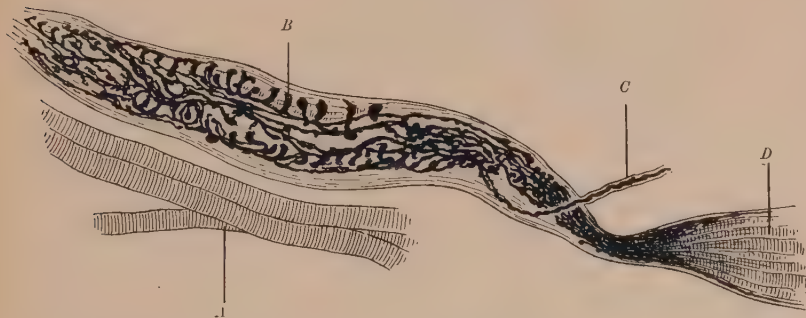
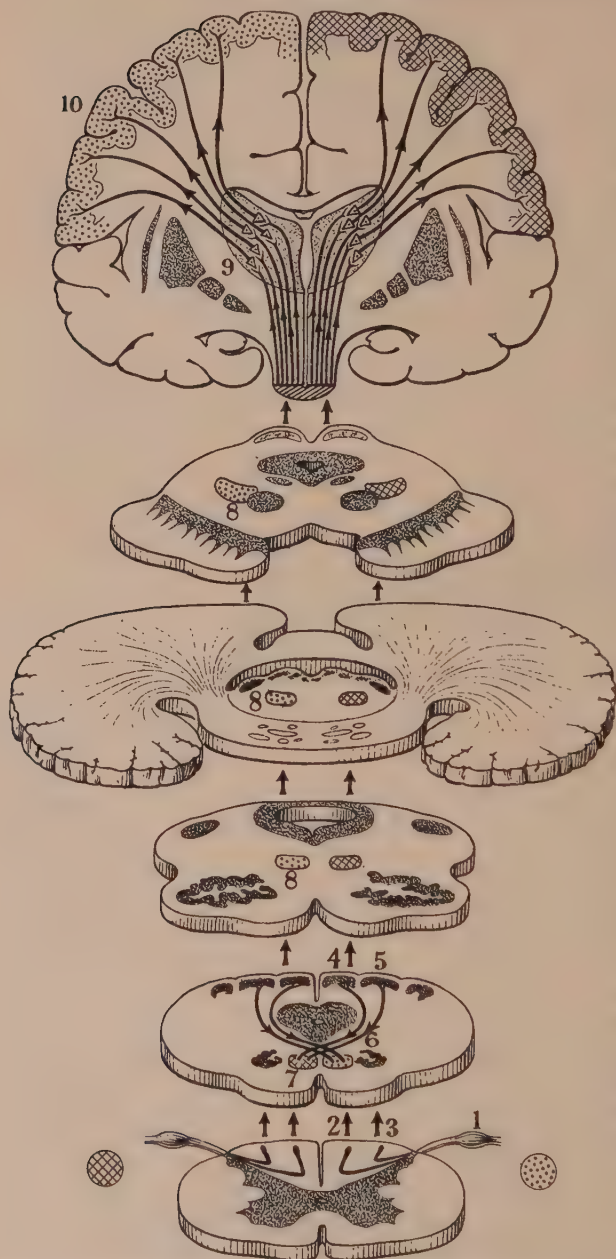


FIG. 104.—A muscle-spindle from a cat. (From a specimen lent by G. Winfield.)
A, ordinary muscular fibres; B, arborisation of nerve-fibres; C, medullated nerve ending in spindle;
D, fine muscular fibres.

for recording the position of one joint surface on another. Muscle-spindles (see Fig. 104) probably record the length of the muscle and the tension in it.

The nerves from the kinæsthetic end-organs are the axons of bipolar nerve-cells situated in the posterior root ganglion. The other axons of these cells enter the cord at the posterior root and arborise round one of three possible second order neurones: (a) those connected with anterior horn-cells of the same or the opposite side, of the same segment or an upper or a lower segment. These are employed for local reflexes such as the knee-jerk; (b) cells in the nuclei gracilis and cuneatus from which the kinæsthetic impulses pass to the lemniscus of the opposite side to travel up in it to the optic thalamus. (See Fig. 105.) Here third order relay fibres start, conveying the impulses to the post-central sensory

LIMB POSITION AND MOVEMENT SENSATIONS



Path ascending to cerebral cortex for conveying sensations of limb position and movement.

The fibres pass through posterior root ganglion (1) to enter the cord. They pass up in the posterior tracts of Goll (2) and Burdach (3) to the nuclei gracilis (4) and cuneatus (5) in the medulla. Having relayed here, the fibres pass across to the opposite side by the sensory decussation (6) to turn up at 7 and form a part of the fillet (lemniscus) (8). In this they ascend to the optic thalamus (9). Having relayed here, fibres convey sensations of limb position and movement to the post-central cerebral cortex (10). It is possible that some skin sensations for touch travel by this route. (See page 253.)

FIG. 105.—Spino-cortical (ascending) pathway for sensations of limb position and movement.

cortex, where those from the legs are distributed at the top, those from the head at the bottom, and the intermediate parts of the body in between in order. In a later section it will be seen that touch, temperature, and pain sensations are distributed in a similar manner, thus permitting correlation between these three great groups of sensory impulses.

THE CEREBELLAR TRACTS.—Kinæsthetic impulses convey highly important information to the cerebellum, enabling it to correlate different groups of muscles, and to carry out orderly limb movements. But since these impulses do not, so far as it is known, reach consciousness, they should not be referred to as kinæsthetic “sensations.” Having entered at the posterior root of the cord, the kinæsthetic fibres arborise round the cells in Clarke’s column. (See Fig. 113.) From here second order relay fibres convey the impulses mostly to the cerebellar cortex of the same side. Most of them travel by the direct cerebellar tract which, passing straight up into the inferior cerebellar peduncle, goes to the vermis. Here the fibres probably relay once more, to be distributed to the cerebellar cortex. Some of the cells in Clarke’s column produce fibres which, crossing the cord to the opposite side, enter the antero-lateral ascending tract (Gowers’ T.). In this they ascend until they reach the level of the red nucleus. They then descend sharply, enter the superior cerebellar peduncle, cross over to the opposite side, and end at the vermis, whence they are distributed to the cerebellar cortex, mostly on the same side as that from which they started. Those from the arms go to the upper surface of the cerebellum, both those which have travelled in the direct and those in the indirect tract. Those from the lower part of the trunk and legs go to the lower part of the cerebellum. Not only, therefore, do kinæsthetic impulses from the right-hand side finish mostly on the right-hand side of the cerebellum, but also they are distributed the same way up, that is, those from the arms finish above those from the legs. The few fibres which cross are probably for the purpose of associating the two halves of the cerebellum, so that proper co-operation of the two halves of the body can be effected. These tracts will be considered again in Section XII of this chapter.

THE APPRECIATION OF POSITION.—A few examples may make clear the importance of the kinæsthetic sensations. A man seated at a table in such a position that he is not able to see his legs or feet can give an accurate description of the positions of both, no matter whether he has placed them there himself or they have been placed there for him. He can take his typewriter, and

if he possesses the necessary skill, he can write at will without watching the position of his fingers in relation to the keys. Such a skilled act requires very precise knowledge of limb position and movement. He must know the positions occupied by the limbs to commence with. He must know the direction in which he wants them to move. He must receive impressions telling him whether they have moved in the required direction. He must estimate the position that they occupy and then commence afresh carefully estimated voluntary movements and so on. Without accurate kinæsthetic information, voluntary control would be equivalent to an admiral sending orders to his ships without any precise knowledge of their whereabouts. A pianist would be unable to read music at sight; quite half the time he would have to be watching the positions and movements of his fingers. It is not voluntary acts alone which require this precise guidance. Such subconscious acts as cycling and roller-skating are accompanied by the reception by the higher centres of streams of kinæsthetic impulses which enable a skater to give a pupil a highly detailed account of the positions of the limbs in time and space. Only such acts as sneezing and defæcating are unaccompanied by such detailed kinæsthetic impulses, probably because these acts can be carried out efficiently without them.

THE APPRECIATION OF RESISTANCE.—When a man pushes a cart he experiences a definite feeling of resistance to his forward progression. It used to be thought that the individual did this by making a careful estimate of the strength of the motor stimuli sent to the various muscles concerned, “the degree of innervation.” This idea may be correct. That there must be additional factors is shown by the fact that a man can form correct estimates of weights placed in his hand when the raising of the weights is carried out by electrically stimulating the biceps muscle. Since he is not innervating the biceps muscle at all, he must estimate the weights by the tensions set up in the biceps muscle-fibres, the biceps tendon, and the pressures exerted between the joint surfaces. These will vary with the mass of the weight. Resistance to motion, that is friction, is probably estimated in a similar manner.

APPRECIATION OF PASSIVE MOVEMENTS.—By measuring the smallest angular movement which individual joints can perceive, and by measuring also the smallest rate of movement that can be perceived, and by multiplying these two factors together, a figure can be obtained which gives the performance of each joint so far as passive movements are concerned. The

values thus obtained show great precision for the shoulder, less for the elbow, less for the metacarpo-phalangeal joint, less for the wrist, and less for the interphalangeal joint. Now if the essential perception in each case is the position occupied by the fingers, it will be seen that the elbow requires greater precision than the wrist and the shoulder greater precision than the elbow, since the elbow has a longer lever attached to it than the wrist and the shoulder a longer one than the elbow. In other words, the performance of each joint should increase in proportion to the length of the lever which it moves. In the following table are shown the approximate lengths of the levers measured in inches which the different joints of the upper limb move. In the second column is shown the performance which those joints should possess in order that the fingers should be moved by each with the same degree of precision. In the last column are given the measured performances of the joints :—

Joint.	Length of Lever.	Expected Performance.	Measured Performance.
Interphalangeal . . .	1	10	11.1
Metacarpo-phalangeal . . .	3.5	2.86	1.56
Wrist	7	1.43	2.04
Elbow	16	0.625	0.5
Shoulder	26	0.38	0.21

A comparison of the last two columns shows that the performance given by measurement corresponds fairly closely with that calculated according to the length of the lever. It is stated that these estimates of passive movement depend more on joint sensibility than on kinæsthetic muscle sensations, on the ground that when tension is applied to the limb which is being moved so as to separate the joint surfaces the acuteness of perception of movement very greatly decreases. It should be noticed, however, that separating the joint surfaces must also stretch the muscles and ligaments, and would therefore materially upset the information which the sensory organs they contained were sending up to the higher centres. For this reason the above evidence does not disprove the view that sensory organs in muscles and ligaments, etc., are contributing their information to those given by the joints.

CONTROL OF REFLEXES.—Kinæsthetic impulses are found to play an important part in reflex action. With intact kinæsthetic pathways an appropriate and co-ordinated motor response results. When this pathway has been cut or damaged, the

movement becomes excessive and inappropriate. This important factor will be referred to again when dealing with reflex action in Chapter XI.

LIMB CO-OPERATION.—Loss of kinæsthetic sensibility not only results in loss of the reciprocal action of antagonist muscles which move any one limb, but also the ability to perform co-operative movements in different limbs, such as are needed to carry out a complicated movement. The finger-nose test is frequently employed for testing the efficiency of limb co-operation. The patient's right hand is extended behind him as far as possible. He is now told to close his eyes. Next he is requested to place his index finger as precisely on the tip of his nose as possible. If he achieves this result it indicates that kinæsthetic sensations from structures about the shoulder are being properly correlated with those from the elbow, etc. A variation of this test is to ask the patient, with closed eyes, to touch named fingers of one hand with the index finger of the other. Another variation is to ask him to touch the toes of either foot with the index finger of either hand.

THE APPRECIATION OF SHAPE.—In normal people the correlation of sight and touch causes ideas to be established concerning the shape, size, position, texture, and visual appearance of external objects. With the eyes shut the sensations from the tips of the fingers and kinæsthetic sensations from the finger-joints co-operate in this shape appreciation. It is of very great utility to the blind.

THE PRESERVATION OF THE ERECT ATTITUDE.—Four different kinds of sensation co-operate in this function: Visual sensations; kinæsthetic sensations from the limbs, sensations from the vestibular organs, and pressure sensations from the soles of the feet. If the eyes be carefully blindfolded, and sensations from the soles of the feet be temporarily inhibited by standing in a freezing mixture, experiment shows that equilibration becomes difficult. The body sways and may fall unless external assistance is given. If three of these sensations co-operate together the erect posture may readily be preserved, but if two of them are simultaneously removed, this feat becomes difficult. When walking or running, particularly along a flat surface, equilibration of the body appears to be an easier process than when standing still. This is probably because the feet can be so placed that they span the vertical line drawn through the centre of gravity. When travelling over an irregular surface, or when tired, or when under the influence of alcohol, the feet are placed further apart on either

side of the body, and the stride decreased so as to give greater stability.

DEFECTIVE KINÆSTHETIC SENSATIONS.—These are met with in the disease locomotor ataxia. They are caused by interference with fibres travelling principally up the posterior roots which are conveying kinæsthetic sensations to the higher centres. The effects in man were vividly described by Starling in the following words: "Attempts to walk simply give rise to a profusion of disordered movements, the legs being thrown in all directions with the patient's efforts, but with no effective result. In such a patient, therefore, walking finally becomes impossible, and with well-nourished muscles and a motor path which is intact he is condemned to pass the rest of his days in bed."

SECTION VI

HEAD POSITION SENSATIONS.—These are of great importance for correct posturing and movement. There are two ways in which they operate: (1) In controlling the poise of the head and the movements it performs in the three planes of space, and (2) in adjusting the position of the head relative to the trunk. In ordinary circumstances three mechanisms preserve the normal head position: (1) vision, and kinæsthetic sensations from the eye muscles; (2) the vestibular organs, and (3) the kinæsthetic sensations from the neck muscles.

Vision plays an important part in head orientation. Suppose that, with the eyes open, the head rotates from its normal position so that the right ear approaches the right shoulder. Then the image on the retina will rotate to the left and will thus inform the higher centres that a tilting movement has taken place and will also notify them of the direction and amount of this tilt. On the other hand, with the head tilted forward, the direction of gaze could only be preserved by some readjustment of the external eye muscles. Those directing the eye upwards would have to contract more strongly, the levator palpebræ superioris muscle would have to contract at the same time to increase the elevation of the upper lid. In consequence of this the muscles and tendons would send to the higher centres different kinæsthetic sensations from those sent when the head is in its normal position. In addition, the brows and cheeks would obstruct the fields of vision in new places. It is very easy to demonstrate the importance of visual judgment. A blindfolded man can be made to lose his balance more easily than one with his eyes open. Animals in whom the vestibules have

been destroyed under an anæsthetic are found subsequently to orientate their heads and to perform skilled movements requiring balance extremely well so long as they can use their eyes. If these are bandaged they fail to do so.

THE VESTIBULAR ORGANS.—Inside the petrous portion of the temporal bone are found the complicated sensory mechanisms which belong to the two entirely different sensations: those of hearing and of head position. The former we shall be dealing with in detail when describing the ear and the perception of

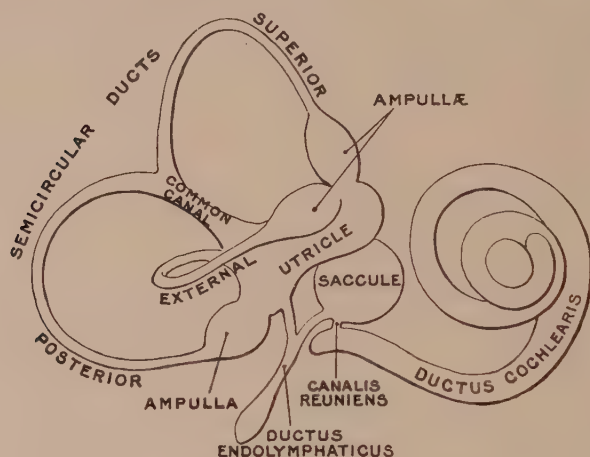


FIG. 106.—The membranous labyrinth. (Enlarged.)
(From Gray's *Anatomy*.)

sounds. With regard to the latter we find that the temporal bone contains a number of canals which communicate with a central chamber—the vestibule. The cochlear canal extends from it on one side and the three semi-circular canals communicate with it on the other. The bony chambers are lined by a thin periosteum and they contain membranous structures which have a shape very like the bony canals in which they lie. Thus each semi-circular bony canal contains a much smaller semi-circular membranous canal, the latter being supported from the former by strands of connective tissue. The space between is filled with perilymph. The vestibule similarly contains within it the saccule, which communicates with the cochlea, and the utricle, which communicates with the semi-circular canals. Utricle and saccule themselves communicate by the ductus endolymphaticus and the canalis reuniens (Fig. 106). The utricle and saccule each contain two sensory maculæ, which

consist of elevations in the mucous membrane, containing large numbers of sensory end-organs. Each sensory cell has a long cilium (which, however, it does not move), attached to which are a number of concretions which are believed to be calcium carbonate. Fibres of the vestibular portion of the auditory nerve ramify in the deeper portions of these hair-cells. Between the hair-cells lie numerous supporting cells. Somewhat similar sensory surfaces, composed of sensory cells and supporting cells, are found near one of the entrances of each of the membranous semi-circular canals. The hair-cells differ, however, from those found in the utricle and saccule in having no concretions. Since there are six canals, there are three of these latter organs in each ear. They are called the organs of the semi-circular canals, whereas those associated with utricle and saccule are called maculæ or otolith organs, from the presence of the concretions on the hairs of the cells.

Nerve-fibres from the five structures in each ear unite to form the vestibular portion of the auditory nerve. The semi-circular canals are arranged in three planes of space at right angles to one another, as shown in Fig. 107. The importance of this will be emphasised in the next section.

FUNCTIONS OF THE VESTIBULAR ORGANS.—

There are two theories concerning these structures.

(1) That the otolith carrying maculæ notify the higher centres of deviations of the head from its normal position. That alter-

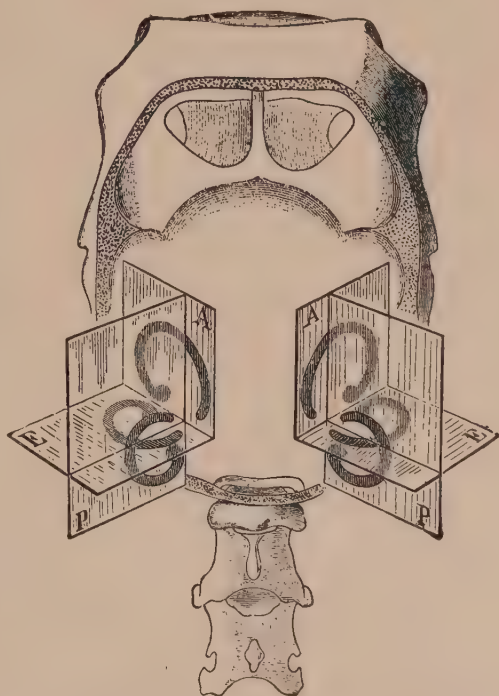


FIG. 107.—Figure showing the situation of the three semi-circular canals in the skull of the pigeon. (From Starling's *Principles of Physiology*.)

A, plane of anterior or superior semi-circular canal; P, plane of posterior canal; and E, that of horizontal canal.

Note that the anterior canal of one side, and the posterior canal of the other side, are in the same place.

natively the semi-circular canals are stimulated by movements of the head in the three planes of space. (2) That the functions of these organs are not so clearly differentiated and are more likely the opposite of those mentioned above. Of these two rival theories the former is the more universally accepted. But upholders of this theory differ about the details in which the mechanisms work. Some say that it is bending of the hairs by the weights of the concretions which brings about stimulation; others that it is the pull of the concretions on the hairs which does so. Similarly, while some consider that one canal responds to a rotation in one direction only, *e.g.* the horizontal canal in the right ear responding to a rotation to the right, while the horizontal canal in the left ear responds to a rotation to the left, others think that each canal is stimulated by both rotations but in opposite senses. Whatever the outcome of these rival theories may be, there is no doubt whatever that the vestibular organs contribute important information concerning the position and movements of the head.

In some of the lower representatives of the animal kingdom, the functions of the vestibular organs are very easily investigated and the results are correspondingly clear. For example, in the crustacea, the otolith organs take the form of a small cell-lined chamber which communicates with the fluid in which the creature lives. A small concretion of sand or lime normally occupies the centre of this chamber, and gravity causes it to press on some of the sensory cells which line it. If the creature inclines to one side, gravity causes the concretion to press on a fresh set of cells, in consequence of which a new set of impulses is sent to the central nervous system. By taking some of these crustacea when they are about to shed their cuticle and by putting magnetic oxide of iron in the water, the otolith organ becomes filled with a magnetic particle in place of the non-magnetic one. On causing an electro-magnet to pull on the magnetic particle upwards in a vertical direction, the crustacea turn over on to their backs. On turning off the current they return to the normal position.

NERVE PATHS CONCERNED.—The vestibular part of the eighth cranial nerve enters the pons between the inferior cerebellar peduncle and part of the nucleus of the fifth cranial nerve, to end at Deiters' nucleus. From here fibres travel to the eye muscles, to the neck, and to the trunk. Those going to the eye muscles produce the nystagmoid movements which are seen in a man when he is rotated in a revolving chair. The movements are of two kinds: those which occur when the movement is commenced, and (if the rotation is continued for a sufficient time) those which

occur when the rotation is stopped. The fibres which convey impulses to the neck and trunk muscles do so by means of the vestibulo-spinal and the Deitero-spinal tract. They cause appropriate movements of neck and trunk so as to preserve the head in its normal position. For example, an animal laid on its side will first bring its head into the normal position, will then rotate its front quarters until they are normal and, lastly, will rotate its back quarters. The normal position of the head is retained when once it has been moved into this position. Fibres also pass to the cerebellum, since this organ is concerned with the complicated interactions of muscles required by equilibrium.

KINÆSTHETIC NECK SENSATIONS.—These are of two kinds, those which are concerned with head poise and those concerned with the position of the head relative to the trunk.

(a) Head poise: If we start with the head in its normal position and incline it slowly we observe an increasing pull on the neck muscles on the opposite side to that to which the head is inclined. The head in its normal position almost balances itself. A slight contraction of the neck muscles first on one side, then on the other, now in front, and now behind, suffices to preserve the poise of the head. The kinæsthetic sensations aroused in the neck muscles as a result of the slight deviations of the head are important because they inform the higher centres if the poise of the head needs correcting.

(b) The position of the head relative to the trunk: This is important, not so much in helping to give us additional information concerning the position of the head, that of the body having been ascertained by other sensory impressions; but rather it is usually employed for giving information of the position of the body, that of the head being ascertained by means of the eyes, the vestibular organs, or kinæsthetic sensations from the neck muscles.

The sensations from the neck muscles travel both to cerebrum and cerebellum. Those to cerebrum relay in nucleus cuneatus, cross in the sensory decussation, go to the optic thalamus of the opposite side, and end in the post-central sensory cortex. Those to the cerebellum travel up in the inferior cerebellar peduncle to end in the cerebellar cortex of the same side.

Two experiments may help to emphasise the importance of some of these sensations. With the eyes open, the individual should have no difficulty in walking along a straight chalk line drawn on the floor, but if he now voluntarily inclines his head well towards one side he will probably find much greater difficulty in doing so. In a second experiment, with the eyes shut, he will find it fairly easy to walk in a more or less straight line, but if the

eyes be closed and the head be held on one side he will find such a feat almost an impossibility.

SECTION VII

CUTANEOUS SENSATIONS.—The skin has two important functions to perform: (1) the preservation and regulation of body temperature, and (2) the perception and classification of the various stimuli which reach it from the environment of the animal

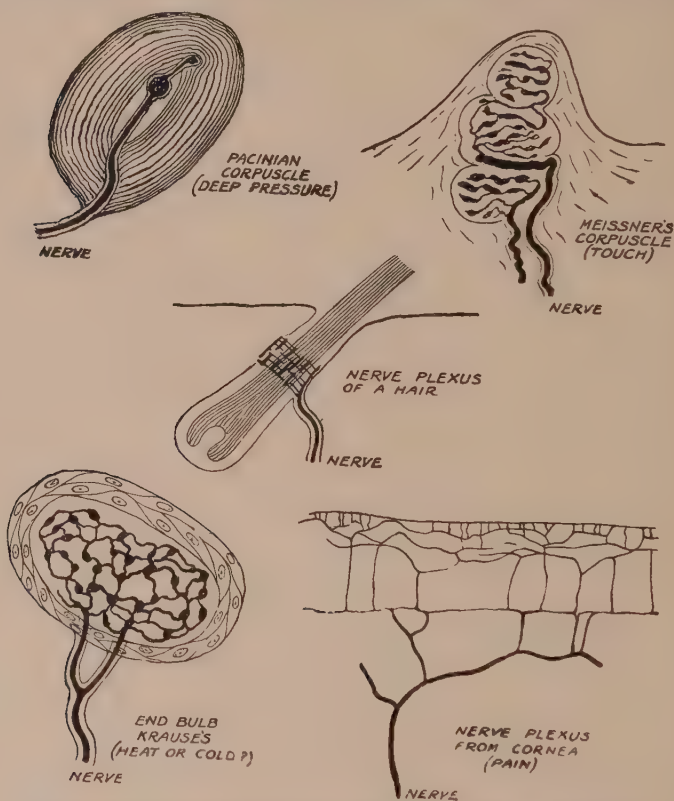


FIG. 108.—Skin end-organs and the probable stimuli they respond to.
(From Starling's *Principles of Physiology*.)

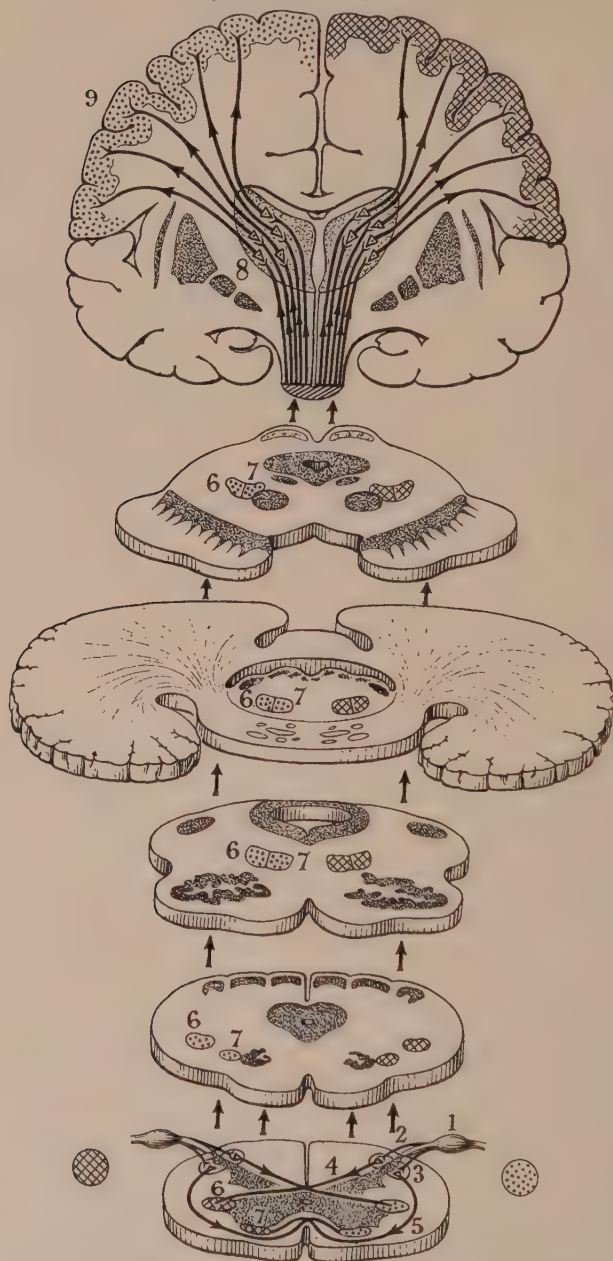
because of its position on the outer surface of the body. The histology of the skin and its heat-regulating aspects will be considered in the special chapter on heat production and regulation (Chapter XIX). Here we will deal solely with its sensory functions. Careful histological investigations demonstrate the existence in the skin of numerous end-organs of extremely diverse

character. According to Botezat there are more than fifteen different kinds of end-organ, many of which can be again subdivided into various types. Broadly speaking, we can describe these as: (a) simple free endings in the epidermis; (b) cellular endings in the epidermis (Merkel's corpuscles); (c) simple free endings in the dermis; (d) capsular endings (*e.g.* Krause's E., Pacini's E., Golgi-Mazzoni's E., and Merkel's E.); (e) encapsulated endings (Dogiel's E., Meissner's E.); (f) end-organs of hairs. It is believed that the free nerve-endings perceive pain, while Meissner's corpuscles are used for touch sensations of the skin proper, the end-organs of hairs being used when external objects touch the extremities of these structures. Krause's endings are supposed to perceive either heat or cold or both. (See Fig. 108.) Pacini's endings, found usually in the subcutaneous tissue are supposed to respond to firm pressure. Owing to the fact that tests performed, *e.g.* by warmed or cooled points, show the existence of certain responsive skin areas which are not only different for heat and cold but are also different for touch and pain, the idea of warm spots and cold spots has originated. This, however, appears to be entirely erroneous. Experiments on succeeding days demonstrate a different distribution for each of the sensations. In other words, they fluctuate not only from day to day, but possibly even from minute to minute. This is probably due to variations in the capillary supply of the skin.

PAIN SENSATIONS.—Originating probably in the simple free endings in the dermis and epidermis, the sensory nerve-fibres pass through the posterior root ganglion, where the nerve-cell of each axon is situated, enter the cord at the posterior root, ascend two or three segments in the short distance of the tract of Lissauer to end at a cell in the substantia gelatinosa Rolandi. Here a second order relay originates; its fibre crosses immediately very near the central canal to enter the posterior bundle of the direct spinothalamic tract. The position of this will be seen from reference to Fig. 109. This tract passes straight up through cord, medulla, and pons, forming in its upper portions an important part of the lemniscus, reaches the optic thalamus, where it arborises round a third order relay cell. The fibres of these cells finally convey the painful sensations to post-central sensory cortex, where they are distributed, legs at the top, trunk in the middle, head at the bottom, as usual.

Pathological changes may involve the path for pain sensations: (a) the first order neurone may get accidentally interrupted, resulting in localised anæsthesia; (b) in neuritis and sciatica the first order neurone may be pressed on or irritated, causing acute

PAIN, TEMPERATURE, AND TOUCH SENSATIONS



Path ascending to cerebral cortex conveying sensations of pain, warmth, cold, and touch.

The fibres pass through the posterior nerve roots (1) and enter the cord. Having ascended a short distance in Lissauer's tract (2) the fibres end at cells in the substantia gelatinosa Rolandi at 3. Having relayed, the fibres conveying temperature and pain impulses travel from here across near the central canal to the opposite side (4). They enter the lateral part of the spino-thalamic tract (6) and proceed up this to the optic thalamus (8) where they relay. The fibres conveying sensations of touch cross at 5 to the anterior part (7) of the spino - thalamic tract. In this they proceed to the optic thalamus (8) where they relay. Both sets of fibres now proceed to the post-central sensory cerebral cortex (9), conveying touch, temperature, and pain sensations.

FIG. 109.—Direct spino-thalamo-cortical ascending pathway for sensations of touch, temperature, and pain.

N.B.—The connections are crossed.

pain; (c) in syringo-myelia the second order neurone may lose its conductivity by the swelling of the central canal of the cord, since the fibres cross very close to this structure; (d) in tabes dorsalis the second order neurone may first be irritated and later be interrupted, and the patient first suffers from lightning pains, later from anæsthesia; (e) in brain injuries or tumours, the third order neurones may be interrupted above the optic thalamus; vague pains of great intensity are described as a result.

HEAT AND COLD SENSATIONS.—It is believed that Krause's end-organs, which are curious knot-like terminations of the sensory nerve inside an oval capsule, are responsible for the perception of both heat and cold. The fibres which originate in these pass by the same route to the cerebral cortex as that taken by the sensations of pain. They are distributed there in a precisely similar manner.

TOUCH SENSATIONS.—Two sets of end-organs appear to be concerned with appreciation of touch: (1) the superficial set, probably formed by the capsulated ellipsoidal Meissner end-organs; (2) a more deeply placed set, probably consisting of Pacini's end-organs. Impulses from these travel up the cord to the higher centres by two routes: (a) in the posterior columns of Goll and Burdach, with sensations of limb position and movement (see Fig. 105); and (b) in the anterior part of the direct spino-thalamic tract. It will be remembered that the former ascend until they reach the nuclei cuneatus and gracilis in the medulla. Here they relay and second order fibres cross in the sensory decussation to the opposite side, where they form part of the fillet, ascend to the optic thalamus, whence third order relays convey the impulses to the post-central sensory cortex. The latter having ascended a short distance in Lissauer's tract relay in the substantia gelatinosa Rolandi, from which second order relay fibres originate, and convey the impulses up the anterior part of the direct spino-thalamic tract to reach the optic thalamus, in which third order relay fibres originate, to end at the cortex. (See Fig. 109.)

It has already been pointed out that kinæsthetic sensations from the skin play a part in the control which results in equilibrium. Thus skin sensations from the soles of the feet give valuable indications, not only to the higher centres so that voluntary movements are properly controlled, but they also convey unconscious kinæsthetic impulses probably to the cerebellum, aiding it in carrying out the synergic control of the limb muscles. These impulses travel apparently in the posterior columns of Goll and Burdach, as far as the nuclei cuneatus and gracilis. Here they

relay, and second order relay fibres now travel as either superficial or deep (or both) arcuate fibres to reach the inferior cerebellar peduncle. In this they now ascend to the vermis of the cerebellum where they relay, and as third order fibres are distributed to the cerebellar cortex. (See Fig. 114 later.)

KINÆSTHETIC SKIN SENSATIONS.—It has already been mentioned in Section V above that the skin sensations play an important part in limb position control. Thus, not only do sensations from the soles of the feet go up to the higher centres and inform us that we are pressing more firmly on one foot than we are on the other, or more firmly on the toes than we are on the heels, but also impulses which are unconscious originate in the skin and underlying structures of the feet and play an important control in the balance of the body. The lack of such sensations not only causes the stamping gait, which is the outward and visible sign that voluntary movements unchecked by suitable kinæsthetic impulses have become inco-ordinated and excessive, but it also causes the exhibition of Rhomberg's sign by the patient, *i.e.* he cannot preserve the erect attitude with his heels together and his eyes shut. That the skin plays an important part in such balance control is shown by the fact that a normal person can be made to exhibit the sign by standing him for a short time in a freezing mixture.

SECTION VIII

POSTURAL REFLEXES.—References have been made more than once to the phenomenon of muscle tone. If we examine an intact animal we see that the muscles of its limbs, particularly the extensor muscles, are in tonic contraction in order to keep the body in an upright position against the pull of gravity. There is, in addition, a certain amount of tone exhibited also by the antagonistic flexor muscles in order to prevent the animal from swaying. If, under an anæsthetic, we remove the cerebral hemispheres, we find that this extensor tone is increased. If now we cut the anterior motor nerve-roots the tone in the muscles disappears entirely, because they are no longer receiving impulses from the central nervous system. If, instead of cutting the anterior roots, we cut the posterior ones, then the tone disappears as it did on cutting the anterior ones. Clearly, then, impulses travelling up to the central nervous system via the posterior roots are responsible. The questions we have to answer are these: In what structures do these impulses originate, and where do they go?

THE STRETCH REFLEX.—If a suitable leg muscle is attached to a recording lever, the existence of this tone may be demonstrated. On an attempt being made to stretch tonically contracted muscle it will be found that the tension which it exerts is very greatly increased. If the kinæsthetic fibres which run from the muscle to the posterior root ganglion be cut, the whole of this tone disappears. It is clear, therefore, that the impulses originate in the end-organs (muscle spindles) of the muscle itself. We have now to describe their subsequent course. Since destruction of the posterior columns of Goll and Burdach results in the disappearance of tone, the fibres must travel by this course. Now the majority of these fibres travelling up Goll and Burdach convey kinæsthetic sensations to the cerebrum. These enable us to say at any moment what positions our limbs occupy. This cannot therefore be the course taken by the fibres which are responsible for the muscle tone that we are considering, because destruction of the cerebrum, far from diminishing the tone, is actually found to increase it, as we have mentioned. It is thought that they relay in nucleus cuneatus and gracilis. From here, second order fibres travel to some at present unknown nucleus. The red nucleus has been suggested, and so has the nucleus of Deiters. From this unknown nucleus, fibres descend to the anterior horn-cells, causing impulses to travel by them to the muscles. At one time it was supposed that the cerebellum was the nucleus at which the kinæsthetic impulses arrived, and from which the tonic ones descended. Many physiologists doubt this. The point will be discussed further when dealing with the cerebellum in Section XIII.

POSTURING MUSCLE RESISTS FATIGUE.—Experiment has demonstrated the interesting fact that posturing muscles do not demonstrate the usual signs of fatigue. One suggested explanation is that the various fibres of which the muscle is composed are taking in turn the duty of preserving the muscular contraction. Suppose the tone necessary for posture to be one-tenth that which the muscles are capable of exerting, then instead of one-tenth of the fibres being permanently in contraction and the remaining nine-tenths permanently at rest, the duty of contracting is undertaken by the different fibres in turn. At any one instant of time one-tenth of the fibres are in contraction, but in succeeding instants different sets of fibres contract, each set being composed of a tenth of the total number. The change from activity to inactivity does not take place simultaneously in all the fibres, but, one or two at a time, certain fibres relax and an equal number of fibres begin to contract. In this way

the work is equalised between all the fibres in the muscle and fatigue is avoided.

THE IMPORTANCE OF HEAD POSITION.—This has already been emphasised in Section VI. It is not surprising to find, therefore, that head position plays an important part in modifying postural tone. An intact animal is taken. By placing a finger under its chin an attempt is made to tip the head up at an angle. The immediate result is increased extensor tone in the fore-limbs, decreased extensor tone in the hind ones, the result being that the animal sits up. If the force applied to the under-surface of the chin be continued, the front paws will leave the ground and the hind-legs will extend until the animal is extended vertically for its full length. The explanation of this modification in postural tone is very simple. The force applied beneath the chin has turned the head from its normal position, but since the chin has been raised the only way that the animal can preserve normal position of the head is by correspondingly raising the neck, and this it does by raising its shoulders and lowering its hind-quarters. Each time the chin is further elevated, the animal elevates its neck to the same degree, thus keeping the head level. Suppose, on the other hand, an attempt be made to bow the head down by pressing on the bridge of the animal's nose. The extensor tone in its fore-limbs will be diminished, thus lowering the animal's neck. If further pressure is applied, both fore-limbs and hind-limbs will lose extensor tone until the animal's body is lying flat. In this instance also the object behind the movements is to preserve the head in its normal position. Experiments performed on animals whose cerebral hemispheres have been destroyed give identical results to the above, showing that the modifications in postural tone are reflex in origin.

EFFECT OF HEAD ROTATION.—Suppose in an intact animal the head be rotated by applying external forces so that the chin is towards the right-hand side and the skull towards the left. Then it will be found that the extensor tonus on the left-hand side is increased while that on the right-hand side is diminished. This has been explained on the ground that this best supports the weight of the head. The more likely explanation is that the animal's legs now exert the necessary forces which will enable its head to be restored to the normal position against the forces which are being applied to it.

FACTORS CONCERNED IN RIGHTING REFLEXES.—Experiments show that the eyes, the vestibular organs, kinæsthetic sensations from the neck muscles, and skin sensations, are all

important factors in causing the righting of the body. Suppose that they were all of them eliminated, no attempt would be made by an animal to right itself. For example, if an animal has its vestibular organs destroyed, its eyes bandaged, its neck placed in a plaster-of-Paris collar, and it be placed on its side on a table, first its fore-limbs and then its hind-limbs will right themselves so that the animal can, if it wishes to do so, get up on to its feet. But if now flat boards be placed along either side of its body, and these be clamped together so that there is equal pressure on both sides, then if it is placed on its side it makes no attempt whatever to right itself. But if the boards be removed and the skin sensations restored, righting takes place. If the eyes be unbandaged, or if the plaster-of-Paris collar be taken off it rights itself. Also an animal with intact labyrinths but with bandaged eyes and neck, and boards clamped at the sides, will be found to right itself like a normal animal. This clearly shows that any one of these factors, sight, vestibular organs, skin sensations, or neck sensations, by itself can bring about righting reflexes. All these experiments, with the exception of those concerning sight, may be performed on an animal whose cerebral hemispheres have been removed under an anæsthetic, with precisely the same result.

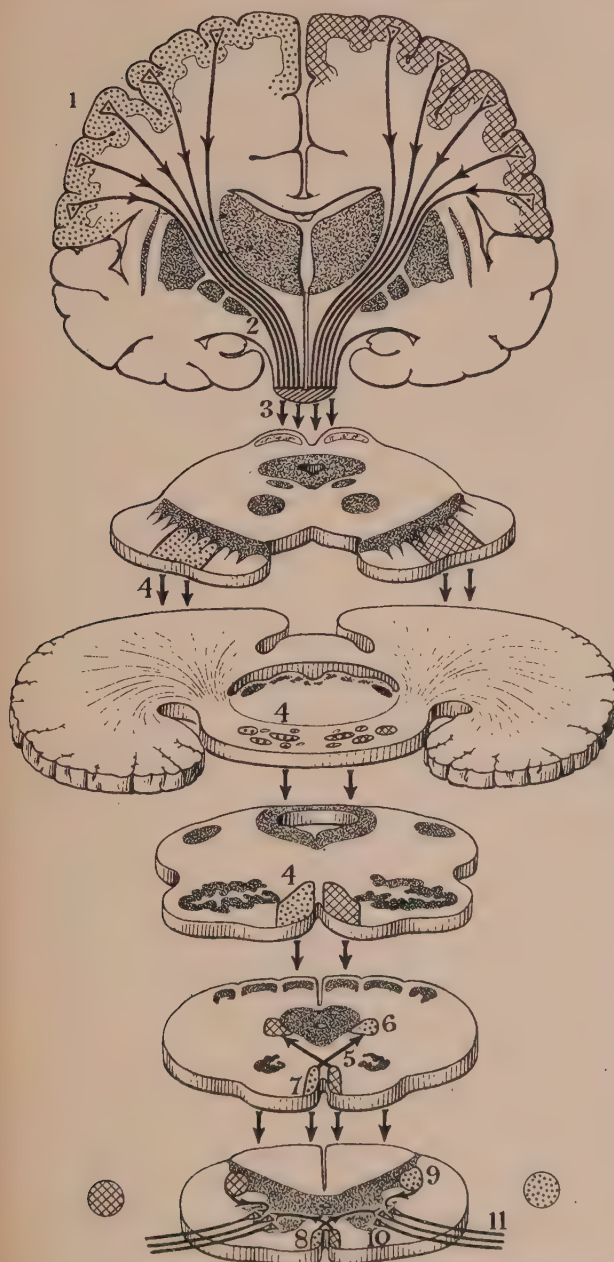
SECTION IX

VOLUNTARY MOVEMENTS.—Histological examination of the praecentral cortex demonstrates the existence of giant pyramidal cells called Betz cells. If any part of this area be stimulated electrically, movements of various kinds occur in the opposite half of the body. These movements are generally quite different from those necessitated by postural tonus. The movements are highly co-ordinated. Antagonistic muscles never contract simultaneously. That there is relaxation of one muscle-group at the same time that contraction of an opposing muscle-group takes place (reciprocal innervation) is shown by the following experiment (Sherrington). Electric stimulation of a small area on the lowest and most anterior part of this praecentral area causes conjugate deviation of both eyes to the opposite side from that to which the stimulus is applied. On stimulating the right-hand side, the eyes turn to the left. If now all the muscles to the right eye be divided except the external rectus, this eye will look steadily towards the right. On now exciting the right cortex, *both* eyes move to the left; the movement of the right eye stops, however, at the middle line, and is simply brought about by relaxation of the right external rectus muscle. (See page 289.)

Not only is the phenomenon of reciprocal innervation exhibited by the limbs when voluntary movement is performed, but also there is inhibition in these same limbs of the postural tonus which they normally exhibit. Thus, postural tone demands contraction of the extensor muscles of the limbs. Decerebration causes an increase in this extensor tonus. On the contrary, stimulation of the cortex produces flexion of both fore- and hind-limb. If various strengths of electrical stimulation are tried, experiment shows that weak currents are much sharper in their localised effects than are strong ones. As the strength is increased, more and more muscle-groups are brought into play until, finally, most parts of the body are involved in epileptiform convulsions. The effects of destroying the praecentral motor area vary with the position of the animal in the scale of development. Thus, in the dog, almost complete recovery takes place; in the monkey there is distinct loss of finger movements, whereas in man the paralysis is practically complete and permanent.

THE PYRAMIDAL TRACTS.—These are made up of the medullated axons of the giant Betz cells of the praecentral (Rolandic) cortex. The fibres from the upper part of the cortex, destined for the spinal centres innervating the leg muscles, run nearly vertically downwards, while those from the lower parts, destined for the medullary centres of the cranial nerves innervating the muscles of the eyes and face, run almost directly inwards. The bundles of fibres from different parts of the voluntary motor area thus converge on one another to form a compact mass which passes down between the optic thalamus and the corpus striatum, constituting an important part of the internal capsule. The bundles belonging to different regions are grouped together as they pass down through the internal capsule in the order in which they occur in the cortex. At the angle of the genu of the internal capsule are placed the fibres to the nuclei of the eye muscles; then follow in turn, face, arm, trunk, and leg. These bundles collect together in a compact mass, and form the middle portion of the descending main pathway which passes through the mid-brain, lying anterior to the substantia nigra. (See Fig. 110.) Retaining the same situation, they reach the pons. They here split up into discrete bundles to permit the cross passage of the pontine fibres. (See Fig. 101 in Section II.) On leaving the pons and entering the medulla they reform into two bundles once more. At the lower part of the medulla the main mass of fibres decussates in the motor decussation to reach a more posterior position; the crossed part is called the crossed pyramidal tract. A remnant of fibres is left behind close to the anterior fissure, which

VOLUNTARY MOVEMENTS



Path descending from the cerebral cortex for voluntary control of muscles.

From Betz cells of the precentral motor cerebral cortex (1) the fibres descending the internal capsule (2), and crura (3), to continue through mid-brain, pons and upper part of the medulla as the cortico - spinal (pyramidal) tract. At the lower end of the medulla the greater part of the fibres pass across in the motor decussation (5), to form the crossed pyramidal tract (6). The smaller part continues towards the cord as the direct pyramidal tract (7). At various levels of the cord fibres from the crossed tract turn off as at 9 to go to anterior horn-cells (10). At various levels of the cord fibres from the direct tract turn off as at 8 to go to anterior horn-cells. Having relayed, the motor fibres proceed to the muscles for voluntary movement via the anterior horns.

FIG. 110.—Cortico-spinal (pyramidal) descending pathway for voluntary control of the muscles.

N.B.—The connections are crossed.

is called the direct or uncrossed pyramidal tract. They descend to the cord in these two situations, passing out at different levels to anterior horn-cells, the crossed ones to cells of the same side, the uncrossed ones to cells of the opposite side. In this way fibres that have originated in the praecentral motor area on the right-hand side of the brain innervate anterior horn-cells, which send fibres to muscles on the left-hand side of the body.

Kinæsthetic sensations can be shown by experiment to play an important part in voluntary movement. If these are defective the muscles tend to over-act, the proper co-operation of muscle-groups is defective, and antagonistic groups of muscles tend to contract at the same time. These facts have been mentioned above in the section on limb position sensations.

HOW MUSCLE TENSION IS CONTROLLED.—We have seen that both muscle and nerve obey the “all or none law.” We also observe that voluntary muscular contraction can be varied at will from the strongest to the weakest. It is necessary to explain how this variation in strength is carried out. Suppose that we dissected out a small motor-nerve and, having cut it, unravelled part of it in such a way that we could apply electric stimulation to any of the 1000 axons it contained. If we stimulated axon No. 1 with a single shock we should obtain a contraction from the muscle-fibre it innervated. If we then stimulated axon No. 2 before the contraction of muscle-fibre No. 1 had begun to die away, and similarly axons Nos. 4, 5, 6, etc., we should produce a weak sustained contraction in which each muscle-fibre in turn played its part. If we wished to produce a stronger contraction we could stimulate simultaneously axons Nos. 1 and 501. Then Nos. 2 and 502 and so on. We could thus increase the strength of the contraction until the whole 1000 muscle-fibres were simultaneously in tetanic contraction. This would necessitate a rapid succession of stimuli to be applied to each of the axons of which the nerve is composed. Adrian has recently shown that voluntary contractions are graded in the above manner.

SECTION X

SPEECH.—This is due to the co-operation of two mechanisms : (1) the production of the voice tone by the lungs and larynx, and (2) the modifications in that tone produced by the resonant chambers of the mouth and throat in order to produce speech. The larynx is placed at the proximal end of the trachea ; it is narrowed at two places by lateral folds of mucous membrane, an

upper pair of false cords and a lower pair of vocal cords. When the latter are brought together and an expiratory air current is driven through them they are thrown into vibration. If appropriately adjusted, a musical tone is the result. Structurally, the larynx is composed of muscles and of a number of cartilages articulating with one another. The whole is lined by mucous membrane, continuous with that of the trachea below and the pharynx above. The principal cartilages from below upwards are: the cricoid, the thyroid, the two arytenoids, and the epiglottis (Fig. 111).

THE MUSCLES.—The cricoid and thyroid cartilages are so articulated that the one can rotate on the other. Such a rotation is brought about by the crico-thyroid muscle. In consequence of this, the arytenoid cartilages are placed at a greater distance from the cricoid cartilage and so the vocal cords are elongated, since they are attached between them. The posterior crico-arytenoid muscle tends to separate the arytenoid cartilages, while the lateral crico-arytenoid muscle tends to approximate them. In addition, the arytenoid muscles tend to hold the arytenoid cartilages together. The thyro-arytenoid muscles, which are embedded in the vocal cords, tend to increase the tension in these cords when they contract. There are, in addition, muscle-fibres inserted into the mucous membrane of the vocal cords, which thins out the substance forming the edge of the cords, and thus permits them to vibrate at a greater frequency. The changes occurring in the larynx during voice production may be observed with the aid of a laryngoscope. This instrument consists of a mirror, A, by means of which a beam of light may be reflected

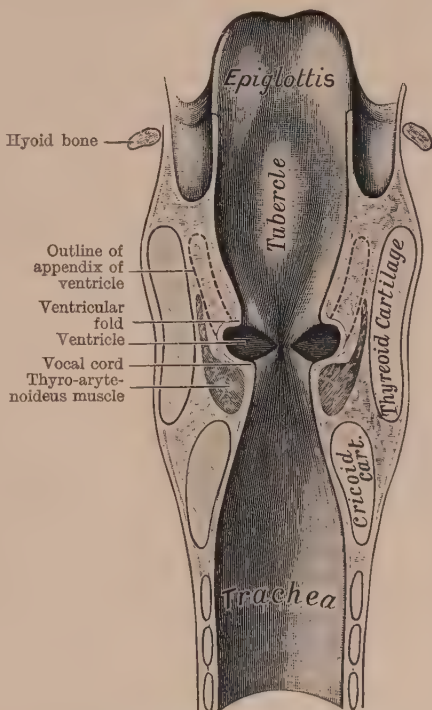


FIG. 111.—Coronal section of larynx and upper part of trachea. (From Gray's Anatomy.)

from a source of light so that it enters the patient's mouth. The doctor now holds a second mirror, B, at such an angle that the beam of light is directed on to the vocal cords. At the same time he sees their reflected image in this mirror B, on looking through a hole in the mirror A.

PITCH VARIATIONS.—Observations show that variations in pitch are brought about in three ways: (1) by modifying the length of the vibrating portion of cord; (2) by varying tension; and (3) by varying mass. Thus, for the lowest register, both cords and arytenoid cartilages vibrate. For the middle register the arytenoid cartilages are rigidly fixed, and the cords alone vibrate. For the upper register the vocal cords are thinned as much as possible by contraction of the membranous portion of the thyro-arytenoid muscle, thus enabling them to vibrate rapidly with the production of very high notes. The average range of pitch of any one individual is usually about two octaves. The female larynx is usually smaller than that of the male, and it is smaller still in boys and girls. Variations in loudness are brought about partly by variations in air-pressure and partly by variations in tension of the cords.

VOWELS are produced by modifying the intensity of the overtones which always accompany the fundamental laryngeal tone. By alterations in the shape of the mouth and throat cavities various overtones are accentuated. Careful analysis shows that some of these, as used in the words, "mat," "met," "mate," and "meat," are produced by the mouth and throat forming separate resonating cavities of various sizes, whereas "moo," "mow," "maw," and "mar," are produced by the mouth and throat acting as a single resonating chamber.

CONSONANTS are classified as dental if they are produced by the tongue on the teeth, *e.g.* "d" and "t"; guttural if they are produced by the tongue on the palate, *e.g.* "g" and "k"; and as labial if they are produced by the lips, *e.g.* "p" and "b"; nasal when the nasal cavity is open as for "n" and "ng"; vibrative when the tip of the tongue is caused to vibrate, *e.g.* "r"; sibilant, which may be voiceless as in "s" or with phonation as in "z."

APHASIA.—The function of speech may really be said to consist of four different mechanisms, two concerning ingoing impressions and two concerning motor mechanisms. The ingoing ones are vision and hearing, the outgoing writing and speech. Eight possible defects may occur: (1) vision may be

perfect and yet written words may mean nothing ; (2) hearing may be perfect but a man may not understand what is said to him ; (3) he may be able to move his hands and yet be unable to write ; (4) he may be able to move his lips and to phonate and yet be unable to speak ; (5) he may be able to read and yet be unable to copy what he reads ; (6) he may be able to read and yet be unable to read aloud ; (7) he may understand what is said to him and be unable to write it down ; (8) he may understand what is said to him and yet be unable to repeat it (it being understood that there is no motor defect to explain (5), (6), (7), and (8)). At one time it was thought that a particular cortical area (Broca's area) was concerned with these functions of speech, injury or disease to this area resulting in aphasia. This view appeared to be substantiated by the fact that right-handed people suffered from aphasia owing to a defect in the left cerebral cortex and *vice versa*. The modern view is, however, that not one but many paths are concerned, and that Broca's area is nothing more than an association area.

SECTION XI

CONDITIONED REFLEXES.—By conditioned reflexes is meant that an individual exhibits particular behaviour under certain circumstances as the result of previous association between them. For example, on placing a dry biscuit in the mouth there is immediate flow of saliva. This is simply cause and effect, and there are no conditions. On the other hand, if, as the result of hearing a gong a number of times the thought of food which it arouses causes a flow of saliva, this is the exhibition of a conditioned reflex, the condition being that the ringing of the gong is always followed by eating. If for several months the gong be rung and, purposely, no food given, by the end of this time the conditioned reflex would have been broken, and no reflex flow of saliva would follow the sounding of the gong. We may say then, that unconditioned reflexes are almost always innate and instinctive, whereas conditioned reflexes are formed as the result of personal habits and experiences, *i.e.* they are acquired. Now it must be understood that different sense-organs could be stimulated and different reflex acts be used for testing the existence of a conditioned reflex. For example, instead of sounding a gong, blowing a whistle, or a draught of wind on the face could equally be used instead. In the same way, instead of the salivary reflex, any other reflex, such as the knee-jerk, reflex acceleration of the heart-beat, or a variety of other reflexes could be used. The

salivary reflex has been used so widely in experimental work on the conditioned reflexes by Pavlov and his co-workers because of the ease with which measurements may be made, and quantitative results obtained. The following table shows the time taken for the development of a conditioned reflex :—

DEVELOPMENT OF CONDITIONED REFLEX TO A TONE OF 637·5 D.V.

Number of repetitions of combined stimuli.	Strength of the con- ditioned reflex when sound tried alone. Drops per 30 seconds.	Latent period of the secretion in seconds.
1	0	—
9	18	15
15	30	4
31	65	2
41	64	3
51	69	2

The above figures show that the conditioned reflex had nearly reached its maximum by the thirty-first repetition. This might be accomplished in a few days by repeating the experiment several times a day.

If conditioned reflexes be established in this way for the smell of camphor and weak electric stimulation of the skin, then it may be shown that, if subsequently both electric stimulation and camphor are simultaneously applied, the number of drops of saliva is approximately the sum of that which either one would give alone. This phenomenon is called summation.

Suppose that a conditioned reflex be established for electric stimulation on a carefully marked area of skin. If subsequently a slightly different area of skin be stimulated, there may be a flow of saliva, but it will only be a part of that which would have been obtained if the correct spot had been stimulated. As spots farther and farther away from the correct area are tried, the number of drops decreases. The fact that some spreading of this kind takes place is called irradiation.

Experiment shows that if a conditioned reflex be established for a particular gong and a gong of different pitch be sounded, little or no flow of saliva will result, according as the difference of pitch be small or large. This is called specificity.

Suppose that two organ pipes of different pitch be sounded alternately, the sounding of one being always accompanied by the giving of food, the other not being so accompanied, discrimination between these two tones can be established. By causing the organ pipes to approach one another in pitch, it is possible to determine at what point discrimination breaks down. Considerable

caution is needed in performing such experiments on animals, because, while the difference between the two sounds may be merely one of pitch to us, there may be other qualities present as well, which are different to the animal. Thus one pipe may emit a slight high-pitched hiss which is above our audible hearing but well within that of an animal's.

Suppose that a dog which has had such a conditioned reflex established in him has for a considerable period not been tested, then on testing him for the first time after, say, two or three months, it will probably be found that the strength of the conditioned reflex has diminished considerably. This phenomenon is called decay. A very few re-applications of the conditioning factors suffice, however, to restore the reflex to its original value. This is called reinforcement.

Now it may be thought that these reflexes concern salivation only, but this is an entirely erroneous idea. The salivary reflex is only used as a convenient indicator of the impulses occurring in the cerebral cortex of the dog. An example will make this point clear.

If on looking out of a window one morning you see a big burly man enter the house opposite and that two minutes later the front door opens and a weeping woman emerges and hurries down the street, you will probably take notice of the fact. If for the succeeding fortnight at the same time, the same thing happens, the arrival of the man and the subsequent emergence of the weeping woman will undoubtedly have become associated in your mind, *i.e.* a conditioned reflex will have been set up. Now suppose that the fifteenth morning is wet, and that at the usual time you see a taxicab draw up at the house opposite and a moment or two later drive away. A little later the emergence of the weeping woman will cause you to think that the man arrived in the taxicab, although you had not actually seen this event take place. This transference of the conditioned reflex from the man to the taxicab is called linking.

But if for the rest of the month you see the woman emerge and the man arrive at the house some ten or fifteen minutes later, comparatively few applications of the events in their new order will suffice to efface your original mental attitude. Exactly the same thing occurs in animals. It is only necessary to ring the gong associated with food a comparatively few times without giving food for the conditioned reflex to disappear. This is called extinction.

SECTION XII

SYNERGIC CONTROL.—The cerebellum consists of two lateral lobes having between them an intermediate lobe called the

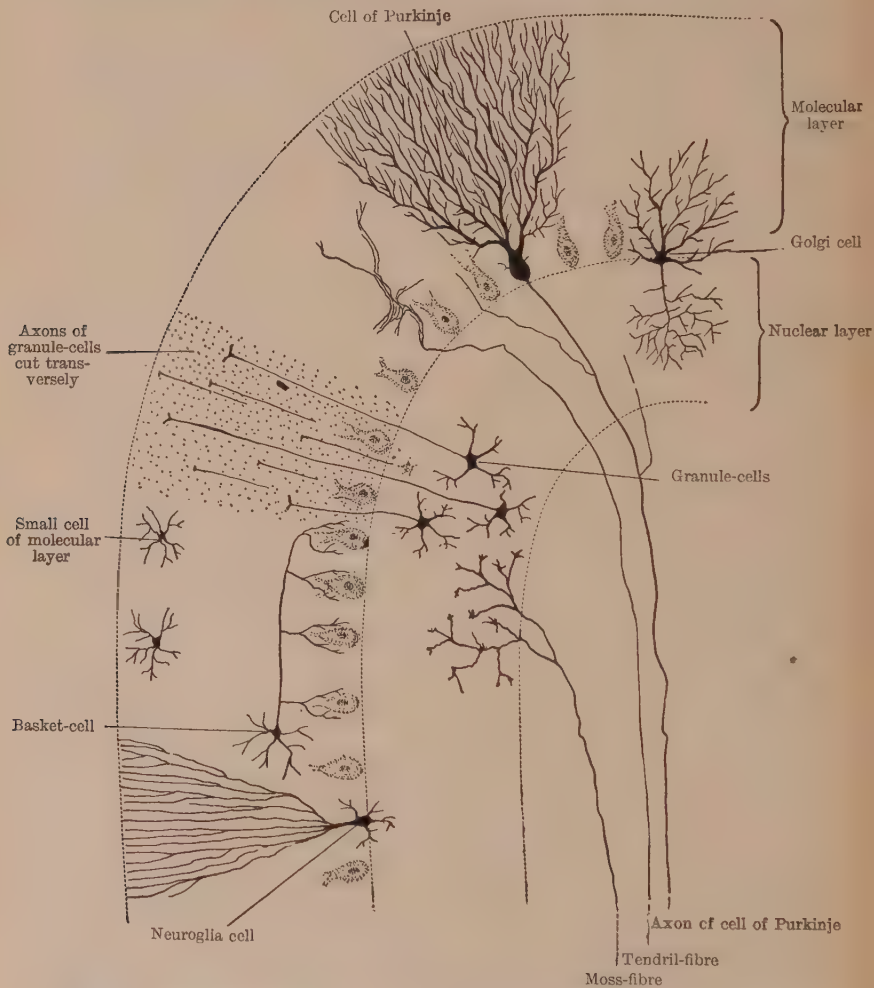
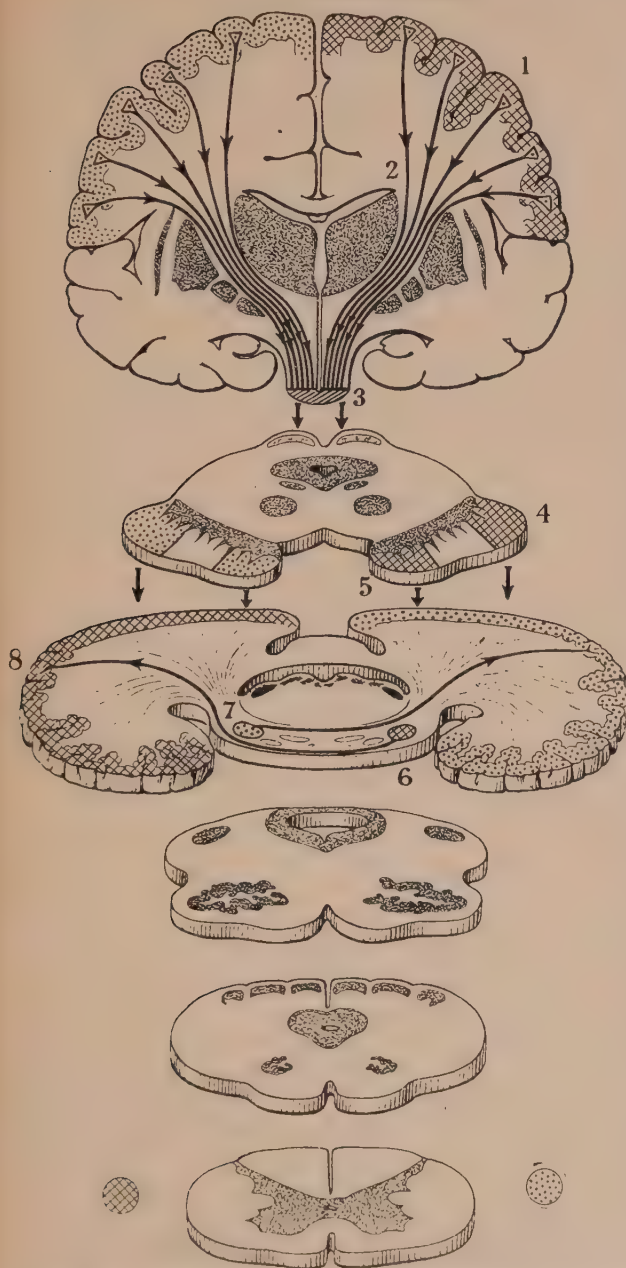


FIG. 112.—Transverse section of a cerebellar folium. (Diagrammatic, after Cajal and Kölliker.) (From Gray's *Anatomy*.)

vermis. Like the cerebrum, the external surface is composed of grey matter with numerous medullated white fibres underneath. It is also thrown into numerous folds.

In its interior are several masses of grey matter, the most

GROUP MOVEMENT



Path descending from the cerebral cortex to the cerebellum for initiating movements of muscle groups.

For voluntary group movements the fibres start at the frontal cortex. For group movements initiated by sight and hearing, fibres start at the calcarine and temporal cortex (1). They descend the anterior or posterior parts of the internal capsule (2). They pass through the crura (3) and the mid-brain. The fronto-cerebellar are shown at 5; the temporo- and calcaro-cerebellar at 4. The fibres end at nuclei in the pons (6). Having relayed, the fibres proceed as at 7 to the cerebellar cortex of the opposite side (8), either directly or via an intermediate relay in the vermis of the cerebellum.

FIG. 113.—Cortico-cerebellar (descending) pathway for the initiation of group movements.

N.B.—The connections are crossed.

important being the nucleus dentatus. The grey matter consists of two layers, an outer molecular and an inner nuclear (see Fig. 112). Where these two layers join there is a single row of large flask-shaped Purkinje nerve-cells. These have numerous dendrons which ramify in a tree-like manner towards the external surface of the molecular layer. In addition, there are found in the molecular layer small stellate-cells, basket-cells, and neuroglia-cells. Golgi cells lie on the junction between molecular and nuclear layers, while the nuclear layer, as shown in Fig. 112, contains granule-cells which send axons into the molecular layer. Impulses enter the cerebellar cortex by two different kinds of termination: moss-fibres in the nuclear layer and tendril-fibres in the molecular layer. The impulses leave the cerebellar cortex by the axons of the Purkinje cells. These fibres partly go to the nucleus dentatus to arborise round the cells there. These cells in turn give off axons which go to the optic thalamus of the opposite side. The rest go to the red nucleus of the opposite side. (See later.) From the red nucleus fresh fibres convey the impulses down the cord to the anterior horn-cells.

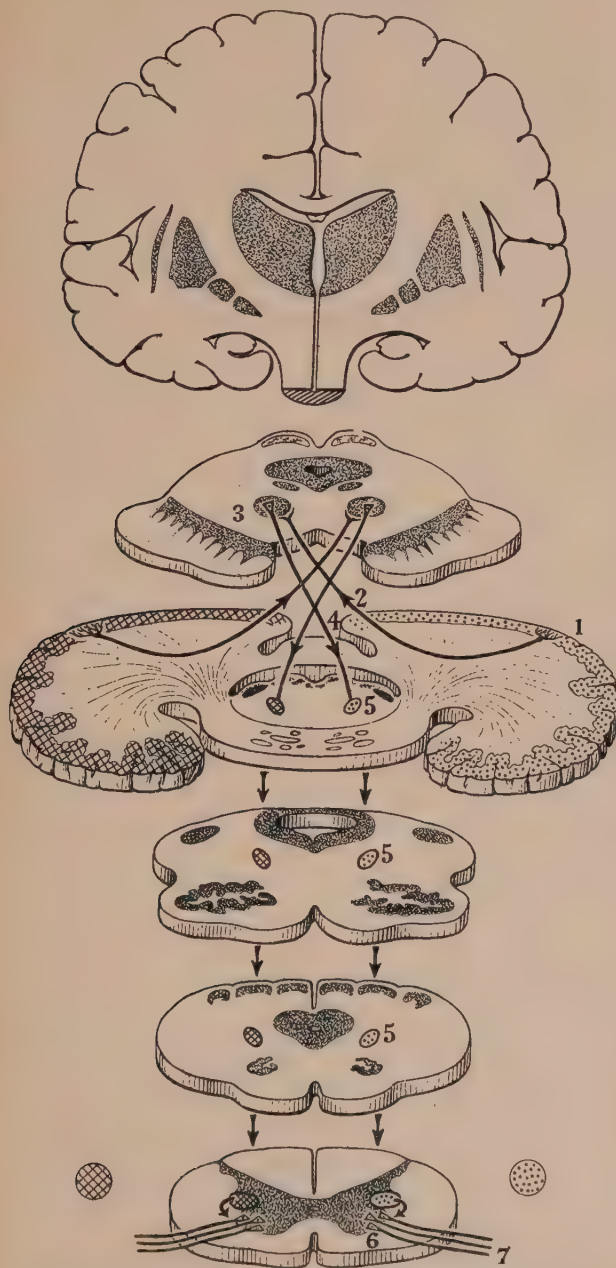
The principal connections of the cerebellum and the way in which they function may be summarised as follows:—

CEREBRUM TO CEREBELLUM.—Voluntary impulses are sent to the cerebellum requiring certain group movements to be carried out. These impulses travel by the fronto-cerebellar and the temporo-calcaro-cerebellar tracts, which descend on either side of the pyramidal fibres. They reach the pons, and end by relaying at cells in it. Second order relay fibres pass across to the opposite side to end at the cerebellar cortex, possibly relaying first at the vermis. By these important fibres the cerebrum sends impulses to the cerebellum. (See Fig. 113.)

CEREBELLUM TO MUSCLES.—Impulses for the carrying out of the required group movements are then sent by the cerebellum to the muscles. Leaving the cerebellar cortex, first order relay fibres travel to the red nucleus of the opposite side through the superior cerebellar peduncles (brachia conjunctiva); here they relay. From the red nucleus, second order relay fibres descend, crossing once more to the opposite side (thus getting to the same side as that from which they started) and descend in the rubro-spinal tract to the anterior horn-cells; from here third order relay fibres convey the impulses to the muscles. (See Fig. 114.)

LIMBS TO CEREBELLUM.—During the performance of the group movements the cerebellum is continually informed of the positions and movements of the limb by kinæsthetic impulses from

GROUP MOVEMENT



Path descending from the cerebellum to the cord for the synergic (group) control of the muscles.

From Purkinje cells (1) the fibres convey the impulses up the superior cerebellar peduncle (possibly relaying in the nucleus dentatus). They cross to the opposite side in the brachia conjunctiva (2), and go to the red nucleus (3). Having relayed, the fibres descend, crossing once more at 4, and descend the medulla and cord in the rubro-spinal tract (5). The fibres turn off at various levels to go to the anterior horn-cells (6). Having relayed, they go as at 7 to the muscles for group movements via the anterior spinal roots.

FIG. 114. Cerebello-rubro-spinal (descending) pathway for synergic (group) control of the muscles.

N.B.—The connections are uncrossed.

muscles, joints, and tendons, which enter the cord at the posterior root and terminate at Clarke's column of cells ; second order relay fibres now convey the impulses up the postero-lateral cerebellar tract of the same side. This goes straight up into the inferior cerebellar peduncle to end at the vermis on the same side, and pass from this to end at the cerebellar cortex in moss or tendril fibres. Some of the axons originating in Clarke's column of cells cross to the other side, and, ascending in the antero-lateral cerebellar tract (Gowers' tract), go up as far as the red nucleus, where they turn down the superior cerebellar peduncles, cross to the same side as that on which they started, and go to the vermis. Here they relay, and as third order fibres are distributed as above to the cerebellar cortex. (See Fig. 115.)

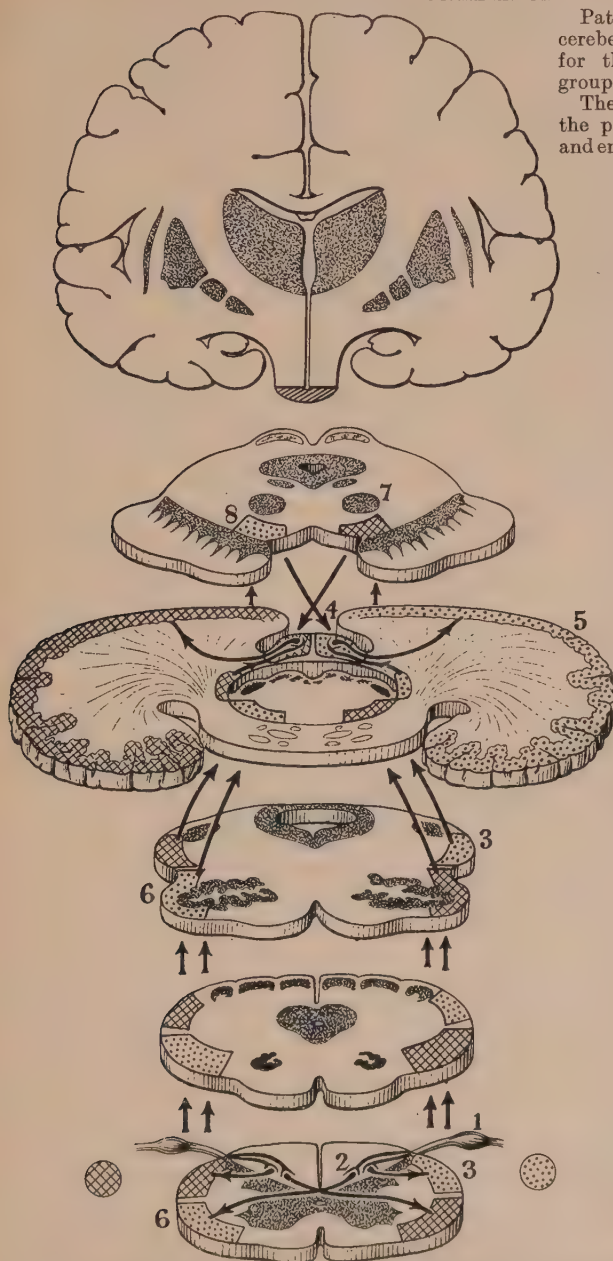
LABYRINTHS TO THE CEREBELLUM.—Important information also reaches the cerebellum from the labyrinths, in order that the poise of the head may be preserved during any group movement involving the body as a whole. These head position sensations from the labyrinths travel as first order relays to Deiters' nucleus, as we have said in Section VI, and, relaying here, travel up as second order relays through the inferior cerebellar peduncle to the vermis, where they once more relay, to travel as third order fibres to the cerebellar cortex.

SKIN TO CEREBELLUM.—In addition, information is sent to the cerebellum from certain important skin areas ; for example, from the soles of the feet. Thus group movements involving locomotion or balance are arrelated appropriately. These skin sensations, having entered at the posterior roots, travel up the columns of Goll and Burdach to relay in the nuclei cuneatus and gracilis. From here, second order fibres pass as superficial or deep arcuate fibres to the inferior cerebellar peduncle of the same side. They travel to the vermis and as third order fibres end at the cerebellar cortex. (See Fig. 117.)

CEREBELLUM TO CEREBRUM.—Lastly, having received information from limbs, labyrinths, and skin showing that the group movements are in correct operation, the cerebellum informs the cerebrum of the fact. From the cerebellar cortex the axons pass to the nucleus dentatus ; here second order relays start and pass up the superior cerebellar peduncle ; they decussate in the brachia conjunctiva to end in the optic thalamus. From here third order relays convey the impulse to the cerebral cortex. (See Fig. 119.)

LIMB REPRESENTATION.—Recent experiments have shown that, contrary to the old ideas, different parts of the cerebellar

GROUP MOVEMENT CORRELATION



Path ascending to the cerebellum from limbs for the correlation of group movements.

The fibres pass in at the posterior roots (1), and enter the cord to end at cells in Clarke's column (2). Starting from these cells most fibres enter the direct cerebellar tract (3); in this they ascend via the inferior cerebellar peduncle to end at the vermis of the cerebellum (4). The fibres from here pass to the cerebellar cortex (5). Fewer fibres, starting from Clarke's column of cells (2), cross to the other side and enter the crossed cerebellar (Gowers') tract (6). In this they ascend until they reach the level of the red nucleus (7). Here they turn down into the superior cerebellar peduncle (8), and cross in the brachia conjunctiva at 4 to end at the vermis. Having relayed, the fibres go to the cerebellar cortex (5). The double crossing causes the impulses to end at the cerebellum on the same side as that on which they started, as do those that have travelled up the direct cerebellar tract.

FIG. 115.—Spino-cerebellar (ascending) pathway for conveying information to the cerebellum of the positions and movements of the limbs.

N.B.—The connections are uncrossed.

cortex are specifically connected with different parts of the body. The upper surface deals with head and neck impulses which are distributed near the mid-line. More laterally are placed abduction and adduction of the arm. On the lower surface we find near the mid-line the areas for the trunk, and more laterally disposed abduction and adduction of the lower limb. These facts are illustrated in Fig. 116. A large series of experiments on the

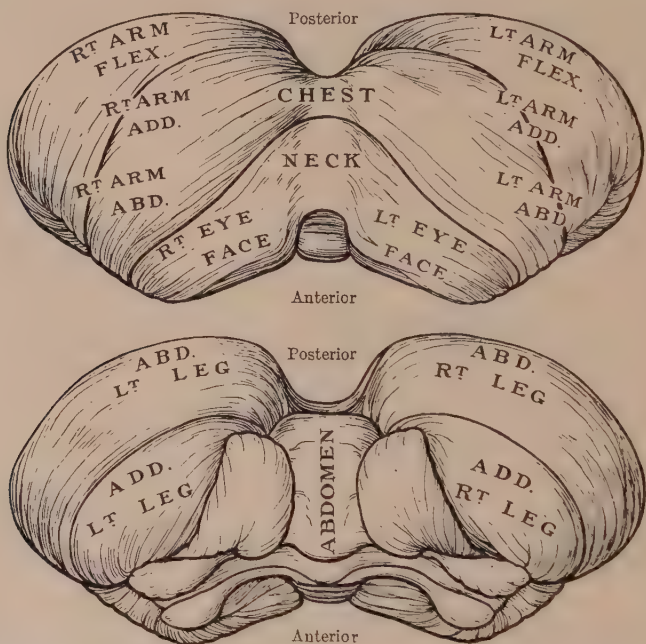


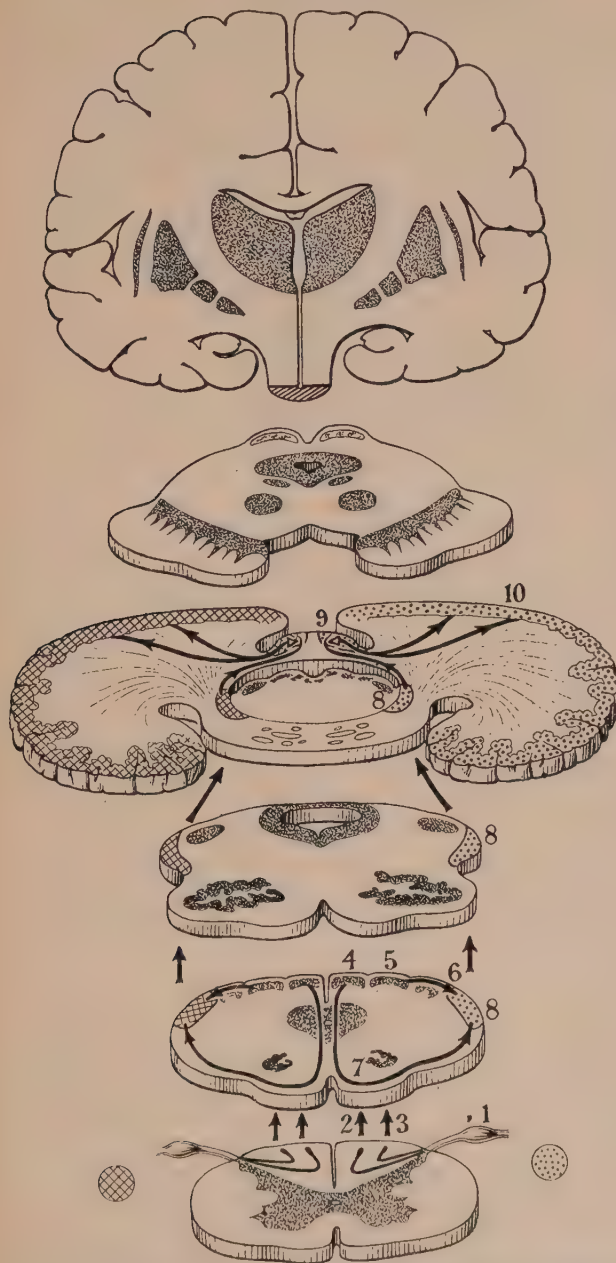
FIG. 116.—Diagrams showing the cortical localisation of the cerebellum. Upper diagram, upper surface. Lower diagram, lower surface.

N.B.—The connections are uncrossed.

extirpation of different parts of the cerebellar cortex in various animals has been made by Bolk and Van Rijnberk. These have demonstrated want of synergic control and loss of tone in various groups of muscles, according to the area of cerebellar cortex destroyed. The effects have been sharply defined.

FUNCTIONS OF THE CEREBELLUM.—Whereas in animals loss of the cerebellum or localised parts of it results in ataxia, asynergia, and asthenia (loss of tone) of the corresponding muscles, in man this is not necessarily the case; on the contrary, loss of the cerebellum or congenital defect of this organ may show no visible sign whatever. An individual who has suffered such a

GROUP MOVEMENT CORRELATION



Path ascending to the cerebellum conveying information from certain skin areas.

The fibres pass through the posterior roots (1), and enter the cord. They ascend in the posterior columns of Goll (2) and Burdach (3), to end at the nuclei gracilis (4) and cuneatus (5). Having relayed, the fibres proceed as superficial (6), or deep (7), arcuate fibres to the direct cerebellar tract (8). By this they ascend into the inferior cerebellar peduncle to end at the vermis (9). Having relayed, the fibres proceed to (10), the cerebellar cortex conveying information from certain skin areas, *e.g.* the soles of the feet.

FIG. 117.—Spino-cerebellar (ascending) pathway for impulses from skin required for group control of muscles.

loss exhibits at first want of synergic control of muscles, but this passes off fairly rapidly. The problem then is this: What precisely are the functions which the cerebellum performs in man? The following is a possible solution. Suppose that for the first time in our lives we try to roller-skate. We find the control of the limbs difficult, but after practice we are able to perform the complicated series of movements required; but as soon as our attention is directed elsewhere or we get tired, this control fails and we fall. Gradually, however, as we become proficient, our limbs begin as it were to control themselves.



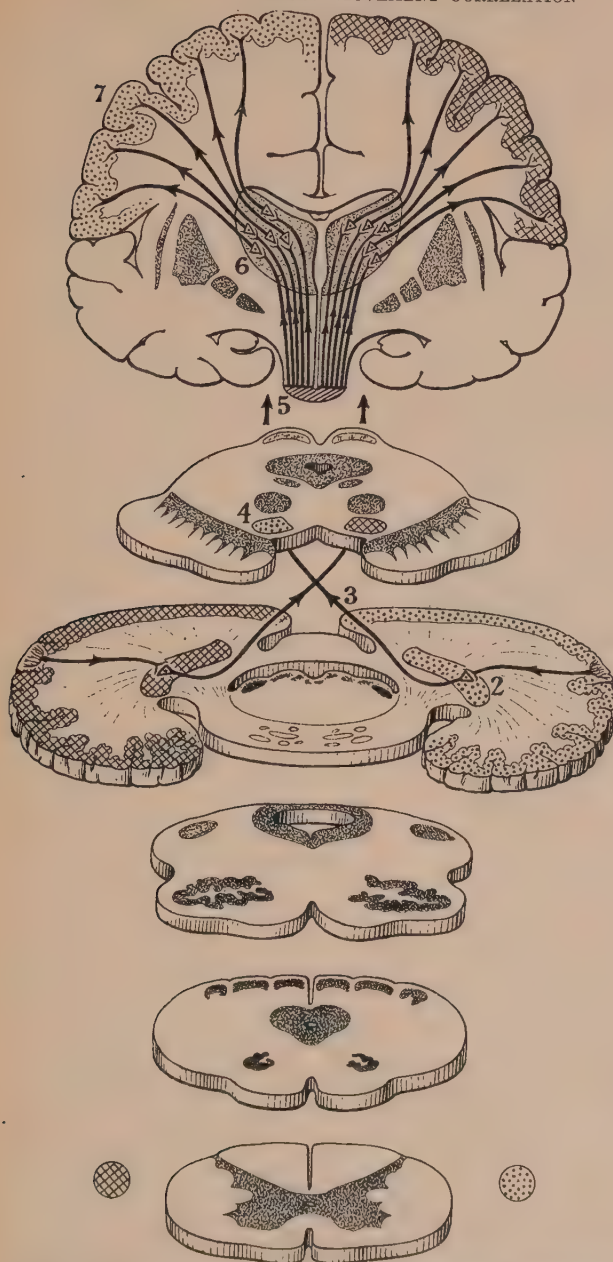
FIG. 118.—Dog with right half of its cerebellum removed.
(From Schafer's *Text-Book of Physiology*.)

Our mind may wander but we do not now fall. With further improvement we find that our higher centres behave as if they controlled a tap. On turning the tap "on" we skate; on turning it "off" we stop. What has really happened is this: at first, every muscle movement had to be controlled by voluntary impulses; but when once these movements were perfected, our cerebellum took over the synergic control of the muscles, so that in time it was merely necessary for suitable impulses to travel from the higher centres to the cerebellum and for the cerebellum in its turn to send out appropriate impulses via the rubro-spinal tract to the muscle centres concerned. We may say, then, that the function of the cerebellum is to relieve the cerebrum of the necessity of giving detailed instruction for the carrying out of acts which are likely to be often repeated. Many of these acts concern equilibration.

SECTION XIII

THE MEDULLA.—This consists, like the mid-brain, partly of a conductor for fibres going up or down the cord, and partly of a system of relay stations for a number of cranial nerves. The most important of these stations, from the point of view of general physiology, are the cardiac, respiratory, and vaso-motor centres. These have already been considered. The medulla also contains, as we have said, the sensory decussation, at the level of the nuclei cuneatus and gracilis, and the motor decussation, at a somewhat lower level. The following summary may be given

GROUP MOVEMENT CORRELATION



Path ascending from the cerebellum to the cerebral cortex correlating their functions.

From Purkinje cells (1) the fibres convey the impulses to the nucleus dentatus (2). Having relayed here, the fibres convey the impulses up the superior cerebellar peduncles to the opposite side by the brachia conjunctiva (3). The fibres then proceed up the cerebro - cerebellar tract (4 and 5) to the optic thalamus (6). Having relayed here, the fibres convey the correlating impulses to the frontal and post-central cerebral cortex (7).

FIG. 119.—Cerebello-cortical (ascending) pathway for correlating the functions of the cerebrum and cerebellum.

N.B.—The connections are crossed.

of the cranial nerves, the levels at which they are found, and their functions. For completeness, those occurring in the mid-brain and pons are included.

The first cranial nerve, the olfactory, will be considered when dealing with smell in Chapter XIII.

The second cranial nerve, the optic, has already been considered in Section III, on Vision, above.

The third cranial nerve, the oculo-motor, will be described in detail in Chapter XII, Section II.

The fourth cranial nerve, the trochlear, which innervates the superior oblique, will also be considered there.

The fifth cranial nerve, the trigeminal, resembles a spinal nerve in having both ascending sensory and descending motor fibres. The ascending fibres, which convey sensations from the face, have their nerve-cells in the Gasserian ganglion; having entered the mid-brain they descend to relay at a long streak of

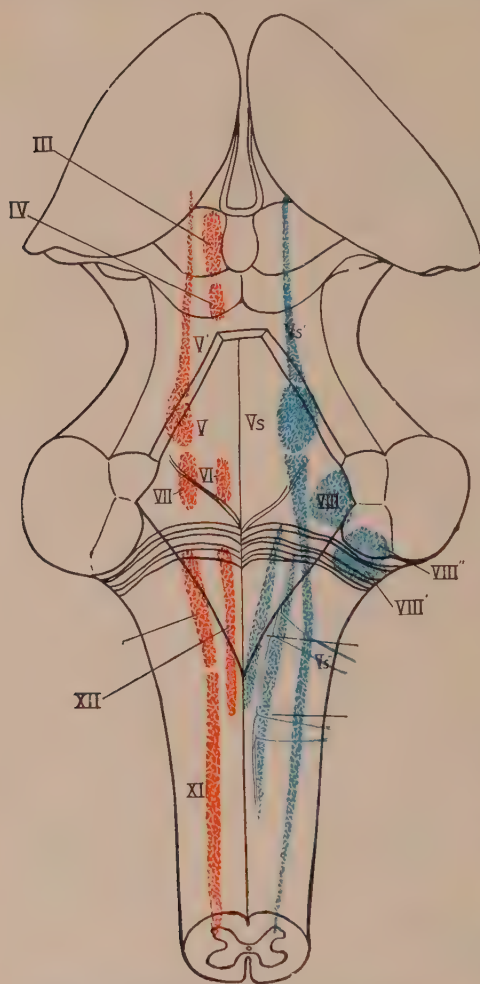


FIG. 120.—A diagram showing the arrangement of the nuclei of the cranial nerves in the brain-stem. Motor nuclei red; sensory nuclei blue. (From Gray's *Anatomy*.)

substantia gelatinosa Rolandi, which goes down nearly as far as the cervical portion of the cord. The second order relay fibres originating there cross to the opposite side and form a part of the lateral fillet. In this they travel as far as the optic thalamus, from which third order relay fibres originate and

convey the impulses to the lower portion of the post-central sensory cortex. The descending fibres originate in the lower and anterior part of the praecentral motor area, they form a bundle of fibres near the genu of the internal capsule, they descend with the pyramidal tract and cross to the opposite side well above the level at which the fifth nerve emerges. They end at the motor nucleus of the fifth nerve, which consists of the homologues of anterior horn-cells. The fibres from these cells descend until they reach the point of emergence of the fifth nerve. They supply all the muscles of mastication.

The sixth cranial nerve, the abducent, supplies the external rectus muscle, and will be found considered in detail in Chapter XII, Section II.

The seventh cranial nerve, the facial, which is the motor nerve to all the muscles of the face, has its nucleus in the pontine region at about the same level as those of the sixth and eighth nerves. Fibres conveying impulses to the facial nucleus rise in the lower part of the praecentral motor cortex, descend near the genu of the fillet, and travel down the pyramidal fibres as far as the seventh nerve nucleus, where they ramify round the homologues of anterior horn-cells from which the seventh nerve-fibres originate. The connections appear to be both crossed and uncrossed, thus causing the two sides of the face to move to some extent together. In addition to supplying the muscles of expression, it also supplies intrinsic and extrinsic ear muscles and a number of muscles of the mouth and soft palate. The submaxillary and sublingual salivary glands and part of the lachrymal gland are supplied by it.

The eighth cranial nerve, the auditory, has already been considered in Section IV above.

The ninth cranial nerve, the glosso-pharyngeal, like the fifth nerve, consists partly of sensory and partly of motor fibres. The sensory fibres have their nerve-cell in the petrous ganglion. They enter the medulla at about the same level as the tenth nerve. Their further course is not known, but they convey sensations of taste from the posterior third of the tongue. They also convey common sensibility from part of the mouth and pharynx. When these are stimulated, they inhibit the respiratory centre. The descending motor fibres originate in the praecentral motor cortex, descend near the genu of the fillet, and relay round the third order cells from which the motor fibres of the glosso-pharyngeal nerve originate.

The tenth cranial nerve, the vagus, is also partly sensory and partly motor. It receives sensations from the pharynx and larynx. These connect with the respiratory centre, so that when the mucous membrane of these parts is irritated, a cough results.

It also receives impulses from the heart and aorta. These cause a slowing of the heart when the arterial pressure rises to excessive values. Sensory impulses from the lungs not only inform the respiratory centre concerning the fullness and emptiness of the lungs, but they also cause reflex constriction of the bronchial muscles when irritants get into the lower air-passages. Sensory impulses from the stomach convey hunger and pain sensations. The tenth nerve also conveys painful sensations from the pancreas and motor impulses to certain pharyngeal muscles, including the constrictors, and to the muscles of the larynx which control the vocal cords. The cardio-inhibitory fibres to the heart and constrictor fibres to the bronchiole muscles travel in it. It causes peristaltic movements in the stomach, oesophagus, and intestine.

The eleventh cranial nerve, the spino-accessory, supplies motor fibres to the trapezius and sterno-mastoid muscle.

The twelfth cranial nerve, the hypoglossal, supplies most of the muscles at the base of the tongue.

SECTION XIV

THE CEREBRO-SPINAL FLUID.—Four membranes are interposed between the bony wall of the cranium and the brain itself: (a) the periosteal layer of the dura mater; (b) the meningeal layer of the dura mater—these separate to enclose the venous sinuses; (c) the arachnoid; (d) the pia mater. The cerebro-spinal fluid lies in the fairly wide space between arachnoid and pia mater. It originates in the tufted and highly vascular chorioid plexuses which are found in the lateral ventricles of the brain. It also originates in the brain substance itself by the leakage of tissue fluid from the capillaries. This passes out through fine membranous tubes which surround the blood-vessel. From the ventricles it passes through the Sylvian aqueduct through the mid-brain to the fourth ventricle, it then passes out through a small hole in the pia mater which covers the fourth ventricle, and thus reaches the cerebral cavity. Having travelled a variable distance in this, it reaches the arachnoid villi which protrude into the venous sinuses. The fluid passes through the thin membrane which separates the sub-arachnoid space from the venous sinuses, and thus enters the blood-stream. The pressure inside the cranial cavity is usually between 60 and 120 mm. of water. If the arachnoid villi become blocked or the chorioid plexuses become enlarged, the intra-cranial pressure rises and hydrocephalus results. The danger of this condition is the interference with the blood supply to the brain which results.

The chemical composition: like lymph, the cerebrospinal fluid contains water, salts, and glucose, but its protein content is lower. It contains oxygen, and may be used as a nutrient medium. It acts as a protecting layer for the brain. In diseases of the brain the protein content increases, cells appear in large numbers, lymphocytes chiefly during tubercular infections, and leucocytes during other types of infection. Chlorides are increased in renal failure.

SECTION XV

SLEEP.—In addition to muscular fatigue which we experience after a period of activity, there is fatigue of nervous origin, the presence of which can be experimentally demonstrated in synapses. Thus, frog's muscle stimulated via its nerve until it will contract no longer, will frequently contract vigorously if electrodes are placed straight on the muscle substance. We are familiar with this nervous kind of fatigue after a long day's work which has not involved any marked muscular exertion. The symptoms are a feeling of heaviness in the head, a dryness of the conjunctivæ, and difficulty in keeping the eyes open. It is found that the body temperature is below normal, and the rate of the heart and respiration are reduced. Muscle tone is diminished, reflexes are prolonged, the thresholds for sight, hearing, and touch are much above the normal. Sometimes there is numbness in the extremities and shivering due to the fall in temperature. During sleep the same depression of the vital functions is displayed. Two alone exhibit an increased activity—the secretion of fluid by the skin and the rate of digestion. The explanation is that under waking conditions the vaso-motor centre is all the time sending down inhibiting impulses which are curtailing the flow of blood to the skin and the viscera. During sleep, vaso-motor control is greatly diminished and the skin and intestines have a free supply of blood. The secretion of sweat and intestinal juices is, therefore, correspondingly aided. By various means it is possible to test the intensity of sleep. One method is to record the blood-pressure and ascertain by experiment how loud a sound is required to produce a noticeable effect. Such experiments show that the depth of sleep increases for three or four hours. It then rapidly diminishes, and becomes much less intense than it has previously been. At this depth it remains until the person wakes. Only three parts of the body do not sleep: the respiratory system, the heart, and the blood-vessels.

THE THEORIES OF SLEEP.—Several theories have been advanced to explain the onset of sleep. Some say that cerebral

anæmia is produced by the fall of blood-pressure which is caused by partial vascular failure. This fits in with the long periods of sleep taken by a person who is suffering from severe hæmorrhage.

Others point to the fall of temperature and say that this is the cause of the diminished heart-output, slower respiration, etc. The lowering of the temperature is, they suppose, due to the exhaustion of local food stores. During sleep these have time to recoup themselves from the liver or the fat depôts. The histological theory of sleep rests on experimental evidence obtained by examining the brains of animals which have intentionally been kept awake for many hours. It is found that the nerve-cells show degenerative changes. The fine terminal ends of the synapse are knobbed and are drawn close to their parent cell. Nissl granules appear to be deficient in such cells (Fig. 121). Sometimes there are minute hæmorrhages into the brain substance. This theory would regard changes in the nerve-cells as the important one. Lastly,

FIG. 121.—Two motor nerve-cells from the dog. (Photographed from preparations by Dr. Gustav Mann.) (From Schafer's *Essentials of Histology*.)

a, normal (note the Nissl-spindles); *b*, after a period of prolonged activity.

there is the chemical theory of sleep, which rests on experiments in which the cerebro-spinal fluid has been removed from animals which have been kept awake until complete exhaustion. This fluid injected into the cranial cavities of normal dogs causes these to show the same symptoms that the fatigued dogs have shown, namely, coma alternating with convulsions.

CHAPTER XI

REFLEX AND AUTONOMIC SYSTEMS

SECTION I

EXPERIMENTS on animals deprived of their cerebral and cerebellar hemispheres show that there is a retention of numerous reflex acts, sometimes of quite a complicated nature. Detailed investigation of these show that they belong partly to the spinal cord and partly to the more peripherally placed chain of nerve-cells and fibres which is referred to as the autonomic system.

THE SPINAL CORD is a cylindrical structure roughly half a metre long. Its functions may be subdivided into: (a) the conduction of impulses to and from various higher centres, *e.g.* the cerebrum, cerebellum, etc., and the cells to which the various spinal nerves are connected; (b) the initiation of reflexes and the preservation of correct nutrition in the muscles and other tissues of the body. Histologically, a transverse section demonstrates that it consists of centrally placed crescent-shaped masses of grey matter which are grouped round the central canal. This grey matter is formed of collections of very numerous nerve-cells. The peripherally placed white matter is composed of bundles of medullated nerve-fibres which are conducting impulses up or down. Since nerves leave and enter the cord in greatly increased numbers at the segments corresponding to the arm and leg, the grey matter is greatly increased at the cervical and lumbar enlargements. On the other hand, the white matter, consisting of conductors, is found progressively to diminish in amount from above downwards. This is because the lower part will contain only fibres connected with the lower parts of the body, while the neck region will contain fibres for the lower part of the body and the upper part as well.

THE SPINAL NERVES separate into two halves as they approach the vertebral column, and enter the cord at two roots, the posterior in-going sensory root and the anterior out-coming

motor root. The sensory root has situated on it, at a short distance from the cord, a swelling which contains nerve-cells. This is called the posterior root ganglion. The cells are bipolar, one axon going to the sensory end-organs, *e.g.* in the skin, the other axon travelling into the cord by the posterior nerve root. It has already been pointed out that when an axon is cut off from its nerve-cell the severed portion degenerates. When cuts are made between the posterior root ganglion and the cord, or between the posterior root ganglion and the peripheral nerve-fibres, the course of degeneration will therefore be that shown in Fig. 122.

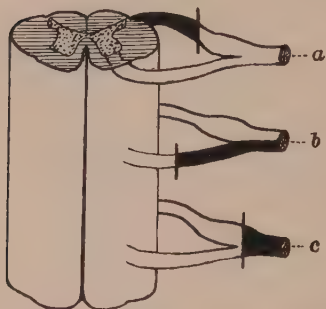


FIG. 122.—Diagram showing effects of section of spinal nerve-roots.

Degenerated portions black. *a*, section of posterior root central to ganglion; *b*, section of anterior root; *c*, section of both roots peripherally to ganglion.

THE NERVE-CELLS in the grey matter of the spinal cord can be divided roughly into four groups: (*a*) the substantia gelatinosa Rolandi, a group formed by nerve-cells close to the posterior horn; (*b*) the cells in the lateral horn from which the axons forming the white rami of the autonomic system originate; (*c*) the cells of the anterior horn in which the motor axons to the muscles originate; and (*d*) the cells of Clarke's column, which are situated on the postero-internal aspect

of the grey matter. These are all indicated by triangles in Fig. 123.

THE NERVE-FIBRES in the spinal cord can be divided into three groups: (*a*) long path axons such as those forming the tracts of Goll and Burdach; (*b*) association-fibres which connect neighbouring segments; and (*c*) commissural-fibres which enable the opposite halves of similar parts of the spinal cord to co-operate. The long-path fibres have already been dealt with under their respective headings in previous sections. For completeness, a résumé of them will now be given.

ASCENDING TRACTS.—(*a*) *Pain, temperature, and touch.* Enter at posterior root; relay at substantia gelatinosa Rolandi; second order cross to spino-thalamic tract; ascend to optic thalamus; third order to cortex (11 and 13, Fig. 123). Crossed.

(*b*) *Kinæsthetic to cortex.*—Enter at posterior root; ascend in Goll and Burdach; relay at N. Cuneatus and N. Gracilis; second order cross in "sensory" decussation, ascend in lemniscus (fillet)

to optic thalamus; third order to cortex (6 and 7, Fig. 123). Crossed.

(c) *Skin kinæsthetic to cerebellum*.—Enter at posterior root; ascend in Goll and Burdach to N. Cuneatus and N. Gracilis; second order travel by superficial or deep arcuate fibres to inferior

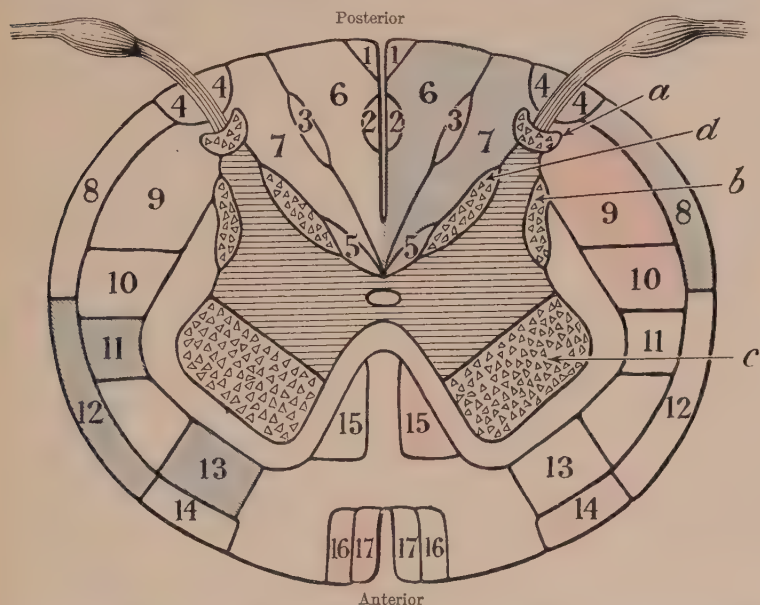


FIG. 123.—Diagrams showing position of tracts of the cord. All coloured tracts convey impulses to or from the right-hand spinal nerve. Ascending tracts are blue. Descending tracts are red.

- (1) Triangular bundle. Short descending tract; (2) oval bundle of Flechsig. Short descending tract for spinal association; (3) comma tract. Short descending tract for spinal association; (4) Lissauer's tract. Short ascending tract for pain, temperature and touch; (5) cornu-commissural tract. Short descending tract for spinal association; (6) posterior column of Goll. Long ascending tract for limb sensation; (7) posterior column of Burdach. Long ascending tract for limb sensation; (8) direct spino-cerebellar tract. Long ascending tract for group movement association; (9) crossed cerebro-spinal pyramidal tract. Long descending tract for voluntary movement; (10) rubro-spinal tract. Long descending tract for group movement; (11) lateral spino-thalamo-cortical tract. Long ascending tract for temperature and pain sensations; (12) crossed spino-cerebellar tract. Long ascending tract for group movement association; (13) anterior spino-thalamo-cortical tract. Long ascending tract for touch sensations; (14) crossed vestibulo- (Deiters') spinal tract. Long descending tract for equilibrium; (15) tecto-spinal tract. Long descending tract for eye protection; (16) uncrossed vestibulo- (Deiters') spinal tract. Long descending tract for equilibrium; (17) uncrossed cerebro-spinal (pyramidal) tract. Long descending tract for voluntary movement.

cerebellar peduncle and thence to vermis; third order to cerebellar cortex (6 and 7, Fig. 123). Uncrossed.

(d) *Muscle, etc., kinæsthetic to cerebellum*.—Enter at posterior root; go to Clarke's column; second order either ascend in direct cerebellar tract to inferior cerebellar peduncle and thence to vermis; third order to cerebellar cortex, or cross to opposite side, ascend in indirect (crossed) cerebellar tract (Gowers') to level

of red nucleus ; descend, crossing in superior cerebellar peduncle to reach vermis ; third order to cerebellar cortex (8 and 12, Fig. 123). Both uncrossed.

DESCENDING FIBRES.—(a) *Voluntary movement.*—Pyramidal tract (cerebro-spinalis anterior) from motor cortex ; second order through internal capsule and pons ; part descends cord as direct pyramidal tract (cerebro-spinalis anterior), near its termination crosses to anterior horn-cells ; third order to muscles. Part crosses in medulla, forming crossed pyramidal tract (cerebro-spinalis lateralis), descends cord, goes to anterior horn-cells ; third order to muscles (9 and 17, Fig. 123). Both crossed.

(b) *Postural movements.*—Rubro-spinal tract (cerebello-spinalis) ; first order from cerebellar cortex crosses to red nucleus ; second order descends crossing in medulla, goes to anterior horn-cells ; third order to muscles (10, Fig. 123.) Uncrossed.

(c) *Equilibrium movements.*—Vestibulo (Deiters') spinal tract ; first order from hair-cells in vestibule to Deiters' nucleus ; second order to anterior horn-cells in cord ; third order to muscles (14 and 16, Fig. 123). Partly crossed, partly uncrossed.

(d) *Eye protection.*—Tecto-spinal. Optic nerve impulses ; first order to superior corpora quadrigemina (colliculi superiores) ; second order to tecto-spinal tract, descend cord to anterior horn-cells ; third order to muscles (15 in Fig. 123). Uncrossed.

(e) *The pupil-dilating fibres.*—These fibres probably originate in the superior corpora quadrigemina (colliculi). They descend as far as the eighth cervical or first dorsal nerve-levels. Here they probably relay at lateral horn-cells, from which fibres pass out at the anterior horn. They travel with the white rami to the first thoracic ganglion, then up the sympathetic chain to branch off to the eyeball, which they enter as either short or long ciliary nerves ; thence in the perichorioidal space to the dilator muscle of the pupil.

(f) *The vaso-motor fibres.*—These travel down the cord from the vaso-motor centre in the medulla by an unknown route. They relay in the lateral horn-cells, from which fibres pass out at the anterior horn to form part of the white rami. These go to the sympathetic chain, where they relay. The non-medullated fibres from these relay cells are called grey rami. They join the spinal nerves and are distributed to the blood-vessels.

(g) *Short-path descending fibres.*—(1, Fig. 123) triangular bundle found in lower lumbar region ; (2, Fig. 123) oval bundle of Flechsig, found in lumbar region ; (3, Fig. 123) comma tract, found in thoracic region ; (5, Fig. 123) cornu-commissural bundle of Bruce, found in cervical region.

COMPLETE SECTION OF CORD.—This results in the following effects: (1) pain referred to parts of the body below section as the result of irritation of cut sensory fibres; (2) increased postural tone in all muscles supplied by nerves below the lesion; (3) complete loss of all true sensations from parts of the body below the lesion; (4) complete paralysis of all muscles supplied by nerves below the lesion; (5) reflexes such as micturition and defæcation become automatic after a period of paralysis; (6) vaso-dilatation below the lesion.

HEMI-SECTION OF CORD.—Hemi-section on the right-hand side will cause: (1) almost complete paralysis of muscles below lesion on right side; (2) increased postural tone and reflexes in muscles on right-hand side below lesion; (3) pain, temperature, and some touch-sensibility is lost on opposite (*i.e.* left) side below lesion; (4) kinæsthetic sensations lost on right side below the lesion; (5) vaso-dilatation on right side below the lesion.

SECTION OF POSTERIOR ROOTS causes: (1) loss of all sensations from limb supplied; (2) inco-ordinated movements of limb supplied owing to loss of kinæsthetic sensations; (3) injuries to skin of limb supplied through absence of protective sensory impulses; (4) complete loss of tone in muscles of limb supplied.

SECTION OF ANTERIOR ROOTS causes: (1) complete loss of muscle-tone in muscles of limb supplied; (2) complete paralysis of muscles of limb supplied; (3) temporary vaso-dilatation in limb supplied owing to cutting of white rami to sympathetic; (4) nutritional disturbances in limb supplied.

PROTOPATHIC AND EPICRITIC SENSIBILITY.—After section of a cutaneous nerve, examination of the area of skin supplied by the nerve reveals (1) a central zone in which all cutaneous sensations are absent, and (2) a peripheral zone in which sensation is either blunted or altered in character, a light touch, for example, exciting a different sensation from that aroused by touching normal skin. Sensations caused by deep pressure are unaffected, showing that these depend largely upon stimulation of afferent fibres in the muscles. During regeneration of the divided nerve, the first sensations to return are those of pain, of heat for temperatures above 38° C., and of cold for temperatures below 24° C.; and these sensations present two unusual features: (1) a stronger stimulus is required to elicit the sensation (*e.g.* that of pain) than in the case of normal skin, but the sensation, when once aroused, is intense, persistent, and

peculiarly unpleasant in character; (2) the power of localising the position of the stimulus is very imperfect.

Some weeks or months later, the sense of touch, the senses of heat and cold between 24° C. and 38° C., and the power of localisation of touch and of pain return, and sensation becomes normal in all respects.

It was suggested that these phenomena are due to the existence of two kinds of sensibility, namely, (1) protopathic and (2) epicritic. Protopathic sensibility, the more primitive, the first to return, includes the sense of pain and that of temperature above 38° C. or below 24° C. Epicritic sensibility returning much later, includes the sense of touch, with tactile localisation, and the senses of heat and cold between 38° C. and 24° C. Recent experimental work has not confirmed the existence of two separate sensibilities since all possible intervening stages are met with.

SECTION II

SPINAL REFLEXES.—In man the reflex functions of the cord are very little in evidence when, as a result of disease or injury, the cord is separated from the brain. It must not, however, be concluded that they are unimportant. Every day experience

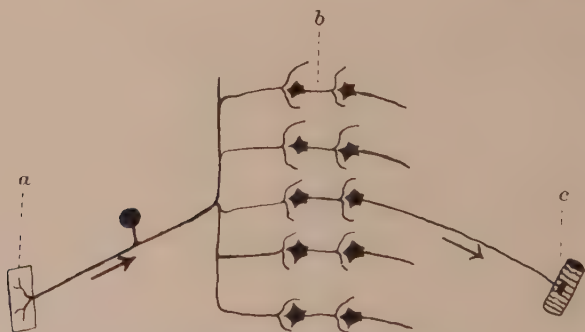


FIG. 124.—Diagram of a reflex arc.

a, receptor; *b*, intermediate neuron; *c*, muscle fibre.

gives examples of reflex acts initiated, *e.g.* by painful stimuli, which have been completed before the higher centres have been fully aware of what has taken place. The structures concerned in the production of a reflex constitute what is known as the reflex arc. They consist of: (1) the sensory end-organ; (2) the sensory nerve (first order relay); (3) a second order relay which conveys the impulse to (4) the anterior horn-cell from which the

third order relay fibre conducts it to (5) the muscle, gland, or other structure concerned. (See Fig. 124.) The time occupied in travelling through such an arc is called the *total reflex time*. Part of this is taken up in transmission of the impulse along the nerves, a part also by the latent period of the muscle or gland. When these are deducted from the total reflex time the reduced reflex time is left. It varies from about a twentieth to a hundredth of a second. It is reduced by increased strength of stimulus.

PROPERTIES OF THE REFLEX ARC.

Since the reflex arc is made up of nerve-cells, fibres, and synapses, it is natural that it should possess the properties which its constituent parts possess. It will exhibit, for example, the phenomena of localisation, inhibition, facilitation, and summation, which have been mentioned in the last section of Chapter III when considering the properties of synapses.

RECIPROCAL INNERVATION.—

When firm pressure is applied to the sole of the foot in a dog deprived of higher centres, there is an immediate extension of the leg. By separating the extensor

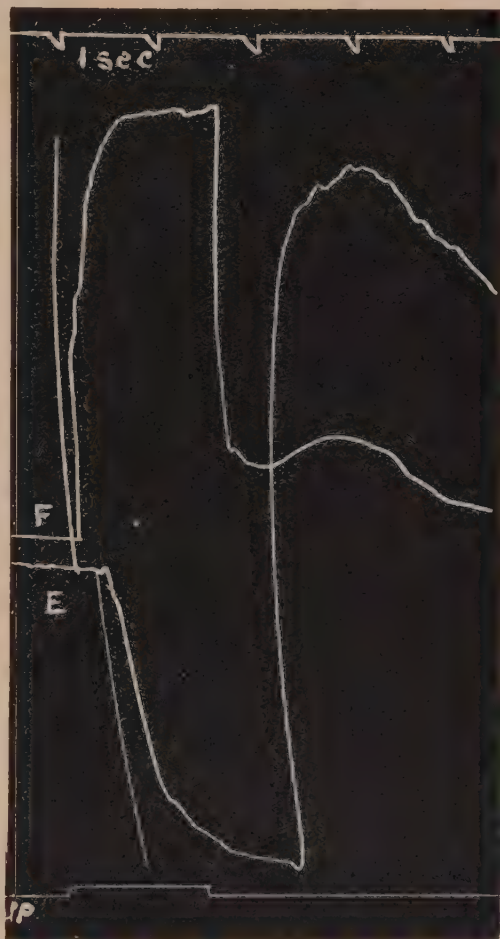


FIG. 125.—Reciprocal reflex of antagonistic muscles of knee (cat). Stimulation of the central end of the (ipsilateral) popliteal nerve (I.P.) causes contraction of a flexor of the knee (F) and relaxation of an extensor of the knee (E). Rise of lever = contraction. (Sherrington.)

and flexor muscles from their attachments to the limb and connecting them to recording levers, it can be shown that the extensor movement was brought about by a contraction of the extensor muscles and a simultaneous relaxation of the flexor muscles. This is clearly shown in Fig. 125. There is ample evidence

that a similar give-and-take relationship exists between all antagonistic groups of muscles. This is spoken of as *reciprocal innervation*.



FIG. 126.—Scratch-reflex temporarily inhibited by application of a painful stimulus to foot. (Sherrington.) (From Starling's *Principles of Physiology*.)

Signal A, stimulation of scratch-area.
Signal B, stimulation of paw by strong induction shocks.

THE SCRATCH REFLEX.—In the normal animal the object of this reflex is the removal of irritant foreign bodies from the area of skin affected. In an animal deprived of higher centres the reflex can be initiated by weak electrical stimulation of a suitable skin area. Separation of the muscles from the leg, the attachment of levers, and the taking of suitable records show that in each movement of the leg the muscles are performing reciprocal innervation movements (Fig. 126). The injection of strychnine, however, causes both flexors and extensors to contract at the same time, and this stops the reflex. This demonstrates the importance of inhibiting the unwanted muscles during the contraction of the wanted ones.

THE FINAL COMMON PATH.

Since the body contains a limited number of muscles whereas the reactions produced by the central nervous system are almost infinite

in variety, it is clear that the muscles must be associated together in different manners for the performance of various actions. For example, flexor muscles of the leg contract part of the time for the performance of the scratch reflex. They also contract when a painful stimulus is applied to the foot. Thus quite different stimuli result in a similar limb movement. This phenomenon is referred to as the final common path.

PREPOTENCE.—The meaning of this term can be readily understood from the following examples : Suppose we stimulate the flank of a dog electrically and thus initiate the scratch reflex. If now a very painful stimulus is applied to the sole of the scratching foot, the scratching movements immediately stop and a flexion of the leg takes place in order to remove the foot from contact with the painful stimulus. One reflex has had prepotence over the other.

UNCONSCIOUS REFLEXES.—The reflexes so far considered may be referred to as conscious in that the higher centres have been fully aware of the nature and extent of the stimulus which set the reflex in operation, and were also fully conscious of the resulting movement. If they approved of it they allowed the reflex to continue, if they disapproved of it they could stop it. The knee-jerk is an example of an unconscious reflex since the higher centres are unaware of the nature of the initiating stimulus. The reflex takes place as follows : With the subject seated in a chair, one leg is crossed over the other. The experimenter now knocks the tendon immediately below the patella, the result being an extension of the leg. The subject feels the blow and he both feels and sees the resulting movement of his limb, but he is quite unaware of the link between the two. The reduced reflex time is of the order of 0·002 second. The path of the reflex is as follows : Originating in the sensory end-organs of the patella tendon, the impulse travels up sensory branches of the anterior cranial nerve (first order relay). The fibres end at second order relay cells which convey the impulses to the anterior horn-cells from which third order relay fibres pass out along the anterior cranial nerve to cause contraction of the extensor muscles of the thigh ; they also travel to the anterior horn-cells of some of the sciatic nerve-fibres, causing reciprocal relaxation of the flexor muscles of the thigh, thus permitting the jerk to take place. The knee-jerk is abolished by cutting the sensory or motor pathways, or by disease of these pathways.

THE EXACT NATURE OF INHIBITION.—It is very easy to show that by exerting voluntary control the knee-jerk can be inhibited. We have ample personal evidence that when we wish to do so we can inhibit practically all the normal reflexes. The closing of the lids which follows the application of a painful stimulus to the cornea may be cited as an exception. It is almost impossible to inhibit this. We must consider how precisely the higher centres carry out this inhibitory process. There are two rival theories : (1) That the conduction of the synapses is

temporarily stopped by applying to them stimuli from the higher centres with a frequency greater than that which the synapses can conduct. Experiment shows that under these conditions the synapses fail to respond to everything, including, of course, impulses which were previously causing the reflex. (2) That a specific chemical substance, *e.g.* lactic acid, is liberated from a precursor in the neighbourhood of the synapse. This substance acts like a local poison to the synapse, so that for the time being it ceases to respond.

SECTION III

THE AUTONOMIC SYSTEM.—In contradistinction to skeletal muscle, the unstriped muscle which is found in the walls of the heart, arterioles, digestive tract, uterus, bladder, and elsewhere, is not under the control of the will, though its contraction is regulated by impulses arising in the central nervous system. The nerves which supply these structures, and also those to the secretory glands, form the autonomic system. The characteristic feature of this system is the existence of a cell-station on every nerve-path between the central nervous system and the effector-organ (muscle or gland). The synapse is situated in a ganglion, and the autonomic path thus consists of a *pre-ganglionic fibre*, a *synapse*, and a *post-ganglionic fibre* (Fig. 127).

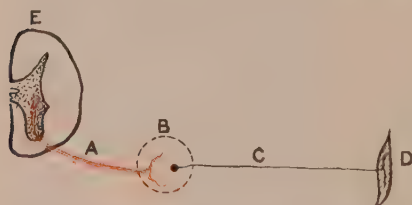


FIG. 127.—Diagram to show relation between pre-ganglionic and post-ganglionic fibres.

E, spinal cord; A, pre-ganglionic fibre; B, cell-station; C, post-ganglionic fibre; D, unstriped muscle-fibre.

The autonomic system includes: (1) branches of the third, fifth, seventh, ninth and tenth cranial nerves, and fibres issuing from the anterior roots of the second and third sacral nerves, and known as the pelvic visceral nerves or *nervi erigentes*; these together constitute the *para-sympathetic nervous system*; and (2) the *sympathetic system*, the pre-ganglionic fibres of which leave the spinal cord in the anterior roots of all the spinal nerves from the first thoracic to the fourth lumbar.

The pre-ganglionic nerve-fibres, being medullated and small, are sometimes called white rami. They vary in diameter from 2 to 4 μ ; each ends by arborisation round a nerve-cell which lies in a sympathetic, or other, ganglion. The axons of the nerve-cells form the post-ganglionic fibres, which, being non-medullated, are called grey rami. The nervous impulse issuing from the central

nervous system along a pre-ganglionic fibre normally passes across the synapse to the ganglion-cell, and then along the post-ganglionic fibre to muscle or gland.

Although the entire autonomic system is built up on this general plan, the actual anatomical distribution of the fibres and the situation of the cell-stations are very varied. The fibres issuing from the brain and the sacral region of the spinal cord have their cell-station close to, or actually within, the organ which they supply. The fibres of the sympathetic system take a different course. Lying along each side of the vertebral column is a chain of ganglia which forms the lateral sympathetic chain. As a rule there is one ganglion corresponding with each spinal nerve-root. But marked variations in detail occur as is seen from Fig. 128.

Nicotine, in small doses, first stimulates and then paralyses the synapses between the pre-ganglionic fibres and the nerve-cells in the autonomic ganglia, thereby preventing the passage of an impulse through the cell-stations; it does not affect the nerve-fibres themselves.

The fibres of the autonomic system supply not only the blood-vessels, but other structures, including the walls of the digestive tract and pelvic viscera, the heart, sweat-glands, and hairs. Their course and function will be fully considered in subsequent chapters, but may be summarised here.

I. *Cranial autonomic fibres.*

Third nerve.—The autonomic fibres pass to the ciliary ganglion, where they have their cell-station, and supply the ciliary and sphincter pupillæ muscles of the eye.

Seventh and ninth nerves.—The autonomic fibres supply vaso-dilator fibres to the tongue, and secretory and vaso-dilator fibres to the salivary glands.

The vagus sends inhibitory fibres to the heart, motor fibres to the muscular coats of œsophagus, stomach, small intestine, and bronchioles, and secretory fibres to the stomach and pancreas; the cell-stations probably lie in the walls of the structures supplied by the different fibres.

II. *Sacral autonomic fibres.*—These supply dilator fibres to the blood-vessels of the penis, and motor fibres to the muscles of the rectum and bladder.

III. *Sympathetic fibres.*

(1) The fibres to the head leave the spinal cord in the first five thoracic white rami, and run in the cervical sympathetic nerve; this contains vaso-constrictor fibres for the blood-vessels, secretory fibres for the salivary glands, and fibres for the dilator pupillæ.

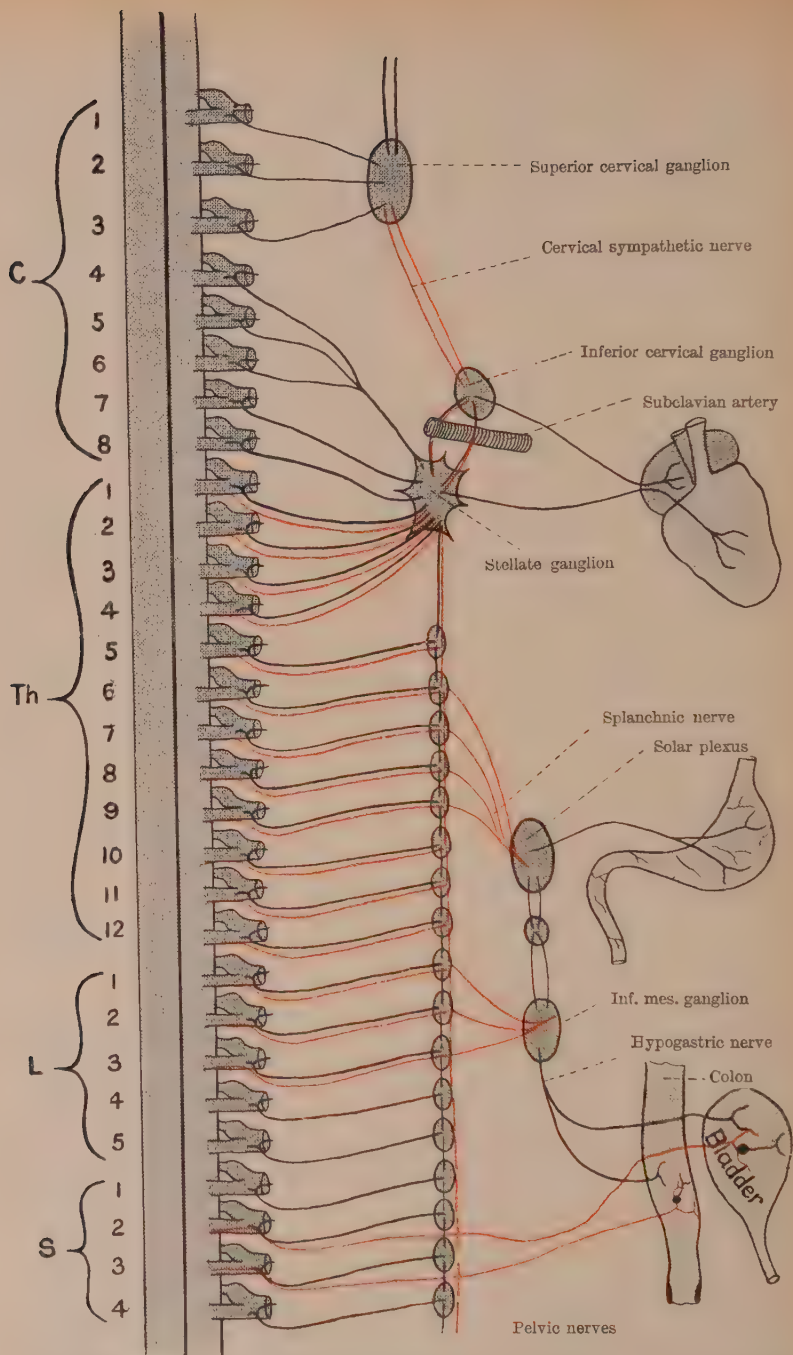


FIG. 128. Diagram of mammalian autonomic nervous system (excluding cranial nerves).

Pre-ganglionic fibres red ; post-ganglionic black.

The fibres forming the lesser and lowest splanchnic nerves in man are omitted in the diagram.

(2) The fibres to the heart have their cell-station in the stellate ganglia, and convey accelerator and augmentor impulses.

(3) The fibres to the abdominal viscera leave the spinal cord in the lower six thoracic and the first lumbar white rami. Most of them have their cell-stations in the semilunar and superior mesenteric ganglia, from which they are distributed. They convey constrictor impulses to the blood-vessels of the stomach, small intestine, kidneys, and spleen, inhibitory impulses to the muscular walls of the stomach and small intestine, and motor impulses to the ileo-colic sphincter.

(4) The pelvic viscera are supplied from the white rami of the last thoracic and the upper lumbar nerves, the cell-stations being in the inferior mesenteric ganglia. The nerves convey constrictor impulses to the blood-vessels of the pelvic organs, motor fibres to the uterus, and inhibitory impulses to the muscular coats of the colon and bladder.

(5) All the white rami also contain fibres which have their cell-stations in the lateral chain of ganglia, the post-ganglionic fibres passing usually, but not always, into the corresponding spinal nerve to be distributed to the blood-vessels of the muscle and skin, and to the sweat-glands and hairs in the area supplied by that nerve.

It will be noticed that many organs are supplied by two sets of fibres, parasympathetic and sympathetic, having opposing functions.

FUNCTIONS OF THE GANGLIA.—The cells of the ganglia serve as distributing centres, and each pre-ganglionic fibre arborises round a number of cells, so that the post-ganglionic fibres are much more numerous than the pre-ganglionic fibres.

At one time various reflex actions were attributed to the sympathetic ganglia, but these have been proved to be not true reflexes, but pseudo- or axon-reflexes. For example, when the nerves connected with the inferior mesenteric ganglion are divided, with the exception of the left hypogastric nerve to the bladder, stimulation of the central end of the right hypogastric nerve causes contraction of the left half of the bladder (Fig. 129). This is due to the fact that certain pre-ganglionic fibres arising in the spinal cord pass through the inferior mesenteric ganglion to form synapses with nerve-cells in the wall of the bladder. In their course through the ganglion each gives off a collateral fibre, which arborises round nerve-cells in the ganglion itself. From these cells post-ganglionic fibres pass to the bladder. Thus, in the above experiment, the ascending impulse set up by the stimulus passes by the collateral fibre in the ganglion to the cell of origin of

a post-ganglionic fibre which is distributed to the opposite half of the bladder. This effect is called an *axon-reflex*.

AFFERENT FIBRES IN AUTONOMIC SYSTEM.—The autonomic system also contains afferent fibres, though these are less numerous than the efferent fibres; in the splanchnic and hypogastric nerves about one-tenth of the fibres are afferent. The stimulation of these fibres by abnormal processes in the abdominal

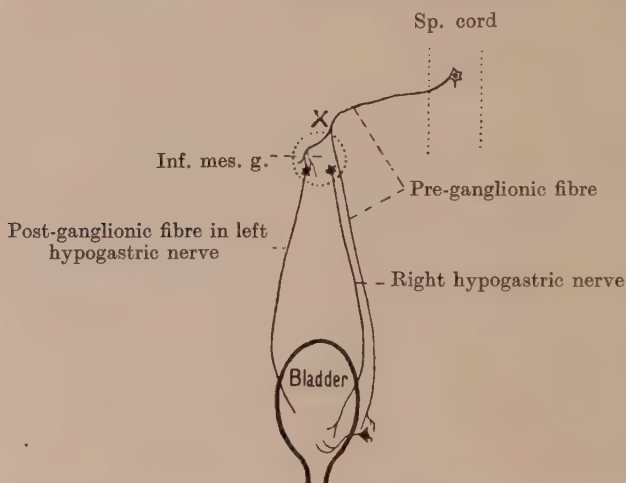


FIG. 129.—Diagram showing the structures concerned in the "axon-reflex" referred to in the text. (From Starling's *Principles of Physiology*.)

organs may give rise to pain. The pain is usually referred, however, not to the organ itself, but to the surface of the body; for instance, afferent impulses from the stomach may give rise to pain which is referred to an area of skin at the lower border of the ribs, and this area may actually be tender to touch. The explanation of this phenomenon is that, where two areas of unequal sensibility are connected with the same spinal segment, any stimulation of the nerve of less sensibility is referred to the area supplied by the nerve of greater sensibility; and the sensibility of the skin is greater than that of the viscera. The position of the referred pain and of tender cutaneous areas has proved of value in man as a means of localising disease of the internal organs.

CHAPTER XII

VISION

SECTION I

PHYSICAL PROPERTIES OF LIGHT.—Light is a form of wave-motion travelling with a velocity of 184,000 miles per second through the ether. It has two characteristic properties, amplitude and wave-length. In the case of ordinary light the whole gamut of waves, varying greatly in length, is present. The wave-length limits are roughly between 7800 and 3800 Ångström units (10 millionths of a millimetre). By means of suitable apparatus it is possible to spread out the constituent rays into a beam in which they are arranged according to their wave-length. They thus form a spectrum. The apparatus for doing this is known as a spectroscope. In the spectrum the colours occur in the following order, starting at the long wave-length end : red, orange, yellow, yellow-green, greenish-blue, blue, and violet. The colours of the spectrum have important properties which form the foundation of the science of colour mixture. Thus, there are certain pairs of colours in the spectrum which are called complementary. When mixed together in suitable proportions they produce white light. We may similarly produce white light by mixing together red, green, and violet ; or orange and yellow by mixing red and green ; or blue by mixing green and violet. But further than this, we can produce all the variety of purple and crimson tints by suitably mixing red and violet. If we start, then, with the three primary colours, red, green, and violet, it is not only possible to produce mixtures which are like the intermediate spectral colours, yellow, orange, green, and blue, but also white and the unsaturated colours, *e.g.* salmon-pink, emerald-green, and turquoise-blue. These properties are independent of theories of colour vision.

THE PHYSICAL PROPERTIES OF MATTER.—Experiment shows that light incident on different materials may be totally

reflected, partially reflected, partly absorbed, diffusely reflected (*i.e.* scattered), or entirely absorbed. Any one of these processes may affect any one part of the spectrum, leaving other parts of the spectrum unaffected. For instance, a polished copper surface reflects practically all the red and orange light which falls on it, while it absorbs the blue-green, blue, and violet. As a result, the light reflected by a polished-copper surface has a typical orange colour; that reflected from gold has also a typical colour. Light incident on the mineral compound vermillion is also selectively dealt with; red rays are diffusely scattered, the blue and green rays absorbed; and light leaving the surface of this material possesses the typical colour of the substance.

Sources of light fall roughly into two classes: those which emit light because they have been raised to a high temperature, *e.g.* the metal filament electric lamp or the carbon particles in a candle; and those which are excited in some other manner, *e.g.* a neon lamp in which the gas neon under a low pressure is set into vibration by the passage of an electric current, practically no heat being produced.

If the spectra obtained from various light sources are compared, it is found that they differ greatly from one another. Usually, sources at a high temperature emit relatively more green-blue and violet light than do sources at a low temperature. Thus, a carbon filament electric lamp, passing sufficient current to be just glowing, will emit considerable amounts of light corresponding to the long wave-length end of the spectrum, *i.e.* red, orange, and yellow light, and comparatively little green-blue, blue, and violet light. If, however, it is heated to the highest temperature it will stand without breaking, by greatly increasing the current passing through it, it will emit a much greater proportion of the short wave-length rays, green, blue, and violet.

The temperature of the sun is much higher than that of any known artificial light. Daylight, therefore, contains relatively greater amounts of shorter wave-length light than do the artificial light sources. In consequence of all this, the colours of objects differ considerably in their brightness under various methods of illumination. Red, yellow, and orange are relatively brighter by artificial light, whereas green, blue, and violet are relatively brighter by daylight.

The part of the spectrum which appears most luminous to the eye is the yellow, but this is not as a rule the part of the spectrum with the greatest energy content. The position of maximum energy is almost always nearer the red end of the spectrum, and in the case of some light is actually in the infra-red.

PHOTO-CHEMICAL CHANGE.—The important principle governing this is known as Draper's law, which states that the chemical change produced is proportional to the amount of light absorbed. Thus, in ordinary photography we make use of the so-called actinic rays, *i.e.* the rays corresponding to the blue, violet, and ultra-violet parts of the spectrum, whereas we make no use of the red, orange, yellow, and green rays. The reason is that the silver substances present in the photographic plate readily absorb the blue, violet, and ultra-violet light, while they are transparent to the red, orange, yellow, and green light. In obedience to Draper's law, therefore, the short wave-length rays produce our photographs, and the red, orange, and yellow rays can be used to illuminate our dark rooms.

SECTION II

THE RECTI MUSCLES.—The eyeball and its accessory structures lie inside the orbital cavity. This is pierced by several apertures through which pass the optic nerve, the ophthalmic artery, the ophthalmic vein, the third, fourth, and sixth oculo-motor nerves and sensory branches from the fifth nerve. The eye is permitted free movement by forming the ball of a ball-and-socket joint. The socket is formed by Tenon's capsule, which is composed partly of connective tissue and partly of smooth muscle. The eye is rotated so that the gaze is turned in different directions by six external eye-muscles. Tendons of these pass through Tenon's capsule in a very ingenious manner so that free movement is permitted, and at the same time the operation of the ball-and-socket joint is not interfered with. Four of the external eye-muscles are called recti and two of them are called oblique. The recti arise from a fibrous ring which is attached to the margin of the optic foramen. They pass forward to be attached to the eyeball a little in front of its equator. From the positions they occupy they are called superior, inferior, external, and internal. Fig. 130 shows the directions in which these muscles turn the gaze. The internal rectus is innervated by the third cranial or oculo-motor nerve and turns the gaze inwards. The external rectus, innervated by the sixth or abducent nerve, turns it outwards; the superior rectus, innervated by the third nerve, directs the gaze upwards and inwards, and the inferior rectus, also innervated by the third nerve, turns it downwards and inwards.

THE OBLIQUE MUSCLES.—The two oblique muscles, the superior and inferior, occupy quite different positions from those of the recti. The superior oblique, having its origin near the optic foramen, passes forward to the upper and inner angle of the orbit. It then passes through a narrow fibrous ring or trochlea, then turns abruptly backwards and outwards to reach the eyeball to which it is attached. When it contracts it pulls the eyeball along a line joining the ear to the bridge of the nose. The axis about which the eyeball rotates is at right angles to this and the gaze is therefore turned downwards and outwards by the pull of the superior

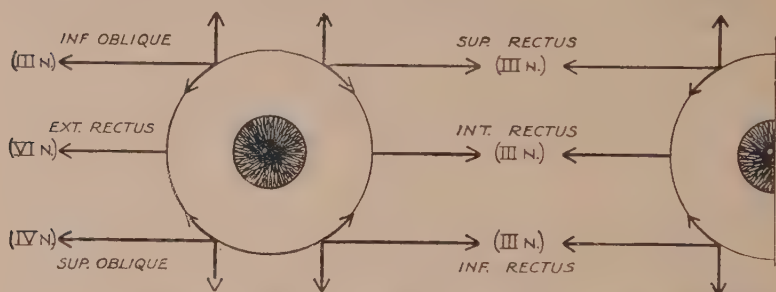


FIG. 130.—Diagram showing the directions in which the external eye-muscles rotate the eyeball. (From Starling's *Principles of Physiology*.)

oblique muscle. The inferior oblique arises from the nasal side of the orbit just within its lower margin. It passes outwards and backwards beneath the inferior rectus, to become attached to the eyeball nearly opposite the attachment of the superior oblique. On contraction the pupil is directed upwards and outwards, as shown in Fig. 130.

A notable feature of the eye movements is the close association which exists between the muscles of the two eyes so that images produced on the retinae by external objects convey a single impression to consciousness.

THE CONVERGENCE REFLEX.—On looking at near objects a certain amount of convergence of the visual axes is necessary. This is usually associated with some accommodation of the lens for near objects and some contraction of the pupil. These combined actions are brought about largely by the close anatomical position of the nerve-cells from which the fibres responsible for these three actions start. Fig. 131 shows approximately the arrangement of the other collections of nerve-cells which are responsible for the movements of the different eye-muscles. It will be observed that the levator palpebrae which elevates the upper lid is in close association with the nerve-centre for the

superior rectus. This permits the upper lid being lifted out of the way when the gaze is directed upwards.

STRUCTURE OF THE EYEBALL.—The eyeball is a sphere about 20 mm. in diameter. The greater part of it is formed by an opaque white membrane, the sclera. In front, this is replaced by a transparent structure called the cornea which has a greater curvature than the sclera. Lining the sclera is the highly vascular and deeply pigmented chorioid. In front, this coat is modified to

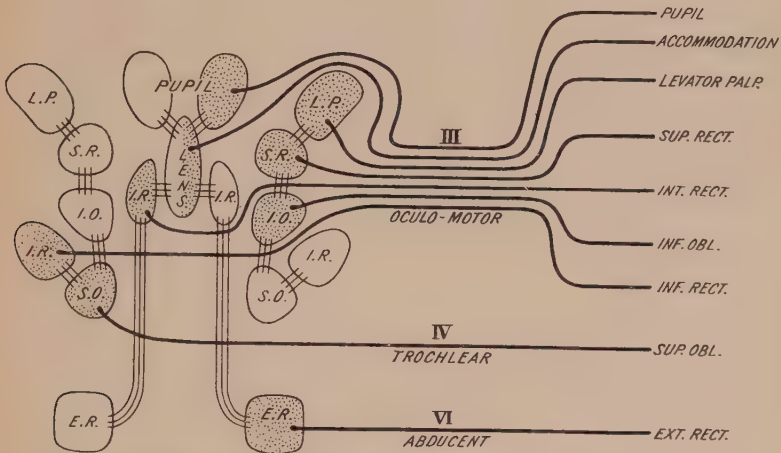


FIG. 131.—Diagram showing the principal connections between the third, fourth, and sixth cranial nerve nuclei. Note the crossed connection of the internal rectus, inferior rectus, and superior oblique. (From Starling's *Principles of Physiology*.)

form the iris, ciliary muscles, and ciliary glands. Spread out within the chorioid is the retina, which contains the pigmented cells and the other important nervous elements for the turning of light into nerve energy, and the conveyance of that energy into the fibres of the optic nerve. The optic nerve emerges at the posterior part of the eyeball slightly to the nasal side.

THE CORNEA.—This is composed of five layers: externally it is covered by a stratified epithelium which is continuous with the conjunctiva. Immediately underneath this lies the anterior elastic lamina of Bowman. Then follows the thick layer of substantia propria. This consists of very transparent white fibrous connective tissue, arranged in layers with intervening cell spaces or lacunæ, which are filled by connective-tissue cells. The fibres are connected by an amorphous cement of nearly the same optical density as the substantia propria, thus forming a medium of nearly

homogeneous structure. To this it owes its transparency. Internal to the substantia propria is the anterior elastic lamina of Descemet. Lastly, there is the layer of endothelium which lines the anterior chamber of the eye. This is formed in front by the cornea, behind by the iris and crystalline lens. The cornea is nourished by diffusion of lymph from a peripheral ring of vessels near the cornea-scleral junction. When diseased, new vessels spring from this and work their way through the substantia propria towards the diseased spot. The nerve supply to the cornea is extremely rich. Enormous numbers of fine nerve filaments which respond to pain are seen ramifying in the external conjunctival layer when specimens of cornea are stained by gold chloride. These connect in the substantia propria with a system of anastomosing fibres from which are conveyed pain impulses via the long ciliary nerves to the nasal branch of the first division of the fifth nerve, thence via the Gasserian ganglion to the fifth nerve nucleus, and thus to the optic thalamus of the opposite side, to reach the post-central cortex, where the sensations are correlated.

THE SCLERA.—This forms the tough external coat of the rest of the eyeball and consists of four layers: (1) a thin layer of endothelium in contact with Tenon's capsule; (2) the loose episclera; (3) the substantia propria, consisting of numerous interlacing bundles of white fibrous connective tissue; and (4) a layer of flat endothelial cells and pigmented connective tissue cells forming the lamina fusca.

In addition to the large aperture in the sclera through which the optic nerve leaves the eyeball, there are small apertures for the short and long ciliary nerves, the ciliary arteries, and the four venæ vorticosæ. At the cornea-scleral junction the cornea and sclera join. A space is however left for the canal of Schlemm. This connects with the anterior chamber (through the spaces of Fontana) and also with the scleral veins. In this way the aqueous humour, which is secreted by the glands of the ciliary bodies and which fills the anterior chamber of the eye at a pressure of approximately 25 mm. of mercury, is permitted to escape through the spaces of Fontana into the canal of Schlemm, and thus via the scleral veins into the venæ vorticosæ, by which it leaves the eyeball. This circulation of aqueous humour is important. Not only does this fluid convey nourishment and oxygen and remove waste products from the crystalline lens and other structures with which it comes in contact, but it also helps to preserve the intra-ocular pressure of the eye at a value of 25 mm. of mercury, independent of variations in blood-pressure.

THE CHORIOID.—This forms the vascular and pigmented lining of the eye. It intervenes between the sclera and retina. Histologically it consists of three layers: (1) the external, similar to the lamina fusca; (2) the substantia propria, which consists of connective tissues richly supplied with blood-vessels; (3) capillaries, veins, and nerves. The vessels are of three sizes, the coarsest external, the finest internal. Internal to the substantia propria is the basilar membrane of Bruch. Immediately next this comes the retina, so that oxygen and nutrient media are able to pass by diffusion from the capsule of the chorioid to the non-vascular layers of the retina. In some animals iridescent pigment cells are found in the substantia propria of the chorioid, and these form a reflecting surface which is called the tapetum. The ciliary glands and muscles of the iris are modified structures developed from the chorioid. The function of the glands is, as we have said, to secrete aqueous humour. The function of the ciliary muscles is to bring about accommodation of the lens for objects at different distances. This will be described in detail in the paragraph on accommodation.

In addition, the chorioid forms the orbiculus, which is a part of the ciliary body connected with the chorioid. The ciliary glands are covered by a thin pigmented layer of cells, which in their turn are covered by a transparent layer of cells. These two layers are developed from the retina. They continue over the posterior part of the iris and are then called the *pars ciliaris retinæ* and the *pars iridica retinæ*.

SECTION III

THE IRIS.—This consists of three layers: (1) The endothelium which is continuous with that described as lining the inner surface of the cornea. (2) The substantia propria of the iris, which consists of connective tissue, especially elastic fibres, two thin sheets of muscle, the anterior of which is arranged circularly so that by its contraction it diminishes the aperture of the pupil. This circular muscle is innervated by the third cranial or oculo-motor nerve (Fig. 132). Behind it is the posterior radially arranged muscle, which by contraction dilates the aperture of the pupil, and is innervated by some fibres which originate from the superior cervical ganglion. (3) The two layers of cells formed by the *pars iridica retinæ*.

FUNCTIONS OF THE IRIS.—The iris controls the quantity of light reaching the retina. It restricts the light rays to the

more centrally placed and the more optically perfect central zones of the lens system of the eye. It also increases the depth of focus of the eye, a factor which is of considerable value in near vision.

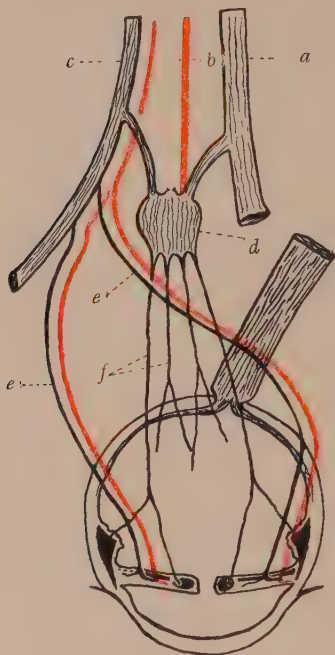


FIG. 132.—Scheme of the nerves of the eye. (After Foster.)

Sympathetic fibres red. *a*, third nerve; *b*, sympathetic root of ciliary ganglion; *c*, nasal branch of fifth nerve; *d*, ciliary ganglion; *e, e*, long ciliary nerves; *f*, short ciliary nerves.

muscle of the pupil are intercepted. The dilator muscle is paralysed, and small pupils which do not react to light are observed in consequence.

(6) When persons suffer from moderate pain.

(7) When the aqueous humour being allowed to escape, the intra-ocular pressure falls.

Dilatation of the pupil occurs :—

(1) When the intensity of light illuminating the retina decreases or when it has a low value.

(2) When the eye accommodates for distant objects.

(3) When any important sensory nerve is stimulated.

(4) During such emotional states as anxiety, fear, etc.

(5) When an individual is suffering from severe want of

Contraction of the pupil occurs :—

(1) When the amount of light reaching the retina is increased, or when it is of high intensity. Contraction occurs within about 0.05 second of the incidence of light on the retina. The pupils of both eyes quickly contract simultaneously and to the same amount.

(2) When vision is directed to near objects. Accommodation of the lens, convergence of the visual axes, and contraction of the pupil occur together, constituting, as we have already mentioned, the so-called convergence reflex.

(3) During sleep.

(4) During mental excitement, the first stage of chloroform or ether anæsthesia, and the first stage in alcohol poisoning.

(5) When injuries to the spinal cord involve the cervical region. The fibres which, leaving the cord, go to the superior cervical ganglion and thus to the dilator

oxygen. This is probably due to the circulation of adrenaline in his blood. (See later.)

(6) During the second stage of chloroform or ether anæsthesia, and in the coma produced by alcohol poisoning.

(7) When the intra-ocular pressure is abnormally high, as in the disease glaucoma, in which the escape of aqueous humour is prevented.

The effects of certain drugs should be mentioned at this point. Morphia and opium, by stimulating the third nerve nucleus, produce pin-point pupils. Pilocarpine and physostigmine produce small pupils by stimulating the third nerve-endings in the sphincter muscle. Atropine and homatropine produce large pupils by paralysing these same nerve-endings. Adrenaline and cocaine produce large pupils by stimulating the same nerve-endings in the radial muscle-fibres.

PROTECTION OF THE EYES.—The upper and lower lids shut and protect the anterior structures of the eye. They are stiffened by two tarsal plates of dense fibrous tissue. Embodied in their anterior surfaces are numerous glands. Some of these secrete a greasy material which, spreading over the margins of the lids, prevents the tear fluid from escaping and rendering the skin inflamed. The lids are closed by the orbicularis palpebrarum muscle, which receives its innervation from the third nerve nucleus, the fibres being distributed with branches of the seventh nerve. Closure of the lids occurs during sleep, if bright light enters the eyes, at the too-near approach of a foreign body, during irritation of the cornea or conjunctiva, when sneezing, and whenever the cornea or conjunctiva become too dry. The conjunctival sac, as the closed chamber formed by the lids is called, is irrigated by the continuous flow of tear fluid which, in addition to the usual salts, has a high bactericidal power. An inflamed condition of the conjunctiva, or the presence of a foreign body in the eye, or an emotional state of mind greatly increases the quantity of fluid secreted. In ordinary circumstances it is siphoned away by two small ducts which open near the internal angle of the eye through two minute apertures, one in each lid. These tubes enter a small sac from which a duct descends and opens just below the middle turbinated bone. The lower end of the duct is closed by a valve, and the sac is periodically emptied by contraction of Horner's muscle.

NUTRITION OF THE EYEBALL.—The blood supply to the eye is very rich. Arteries come in: (a) with the optic nerve-sheath; (b) as long posterior ciliary arteries; (c) as short posterior

ciliary arteries ; (*d*) as anterior ciliary arteries which are branches from the muscular vessels ; (*e*) as conjunctival arteries. These pierce the sclera and freely anastomose with one another in the chorioid and ciliary bodies. Two concentric vessels are formed in the iris, the *circulus major* and *circulus minor*. Between the two pass a number of radial arteries. The retina depends for its blood supply partly on diffusion from the very rich layer of capillaries formed on its outer side by the chorioid. In addition, its inner surface is supplied by fine but highly important vessels which are branches of the central artery of the retina. Other structures, notably the transparent optical media of the eye, depend on the flow of aqueous humour and diffusion from neighbouring structures for the maintenance of their nutrition.

SECTION IV

THE OPTICAL SYSTEM OF THE EYE.—Four structures are principally concerned : cornea, aqueous humour, crystalline lens, and vitreous humour. The histology of some of these structures has already been considered.

The crystalline lens is a bi-convex transparent elastic body enclosed in a capsule. To the periphery of this are attached suspensory ligaments, which in their turn are attached to the ciliary bodies by ligamented portions of the zonule of Zinn. In this manner the lens is held firmly in place and, as we shall see, tension is placed upon it by the pull of the ciliary bodies. The lens is composed of a number of radially arranged epithelial cells. The more peripheral are softer and of lower refractive index than the more centrally placed, which form a comparatively dense non-nucleated mass. Since refraction occurs when light passes from a medium of one optical density into a medium of another, refraction will take place when light becomes incident on the cornea. Refraction will also occur when light passes from the aqueous humour into the crystalline lens. The crystalline lens, owing to the change of refractive index on passing from the periphery towards the central nucleus, behaves as a more powerful lens than it would do if it were replaced by one of uniform structure having a refractive index equal to the mean of the various parts of which it is composed. Thus, the refractive index of the periphery of the lens is 1.37 ; that of its nucleus is 1.41, the mean being about 1.385 to 1.39. But a lens of the same shape as the crystalline lens required to produce the same refracting power would have to be given a refractive index of 1.42. Calculation shows that the accommodation of the eye, which is produced, as we shall see later, by changes in

the shape of the crystalline lens, has its range approximately doubled by this curious structure of the crystalline lens. Fig. 133 shows diagrammatically how an external object gives off light rays, which pass through the lens system of the eye to produce a sharply focussed image on the retina. It will be observed that the retinal image is an inverted one. There

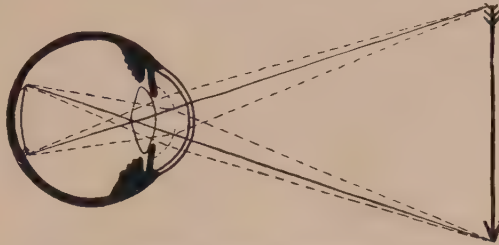


FIG. 133.—Diagram showing formation of an image in reduced eye.

is overwhelming evidence to confirm the accuracy of this fact :—

(1) The analogy of the photographic camera.

(2) If the eyeball of an albino rabbit be carefully excised, and then suitably mounted in front of a brightly lit screen on which has been drawn a boldly marked black and white diagram, observation of the posterior part of the eyeball will demonstrate the existence of the image formed by the lens system of the eye, and it is clearly seen that this is inverted.

(3) It is possible for a student to test the matter for himself. If, with the eyes shut, the tip of the little finger of the left hand be pressed against the margin of the upper lid as near as possible to the outer angle of the orbit of the left eye, a black spot surrounded by a narrow bright ring will be observed in the extreme right-hand field of the left eye. That is, pressure applied to the left side of the eyeball producing mechanical stimulation of the retina lying inside causes an effect which is seen in the field of vision on the right-hand side. This conclusively proves that rays of light passing from the right side arrive on the left side of the retina. In a similar manner it can be shown that rays from the left-hand side arrive on the right-hand side of the retina. That is to say, the rays cross on their way through the lens system of the eye.

ACCOMMODATION OF THE EYE.—There have been at least four theories to explain the power of the eye to focus clearly distant objects or near objects at will: (a) that there is an increase in the curvature of the cornea; (b) that there is elongation of the eyeball; (c) that the lens during near vision comes closer to the cornea; (d) that the lens changes in its curvature. All these theories have been disproved except the last one.

Critical measurements of the images reflected off the anterior

and posterior surfaces of the crystalline lens show that both surfaces have a smaller radius when the eye is accommodated for near vision. They show, moreover, that the anterior surface suffers the greater change.

	Distance.	Near.
Radius of anterior surface .	10	6
Radius of posterior surface .	6	5.5
Thickness of lens . . .	3.64	4
Focus of lens in mm. . .	44	30
Focus of lens in dioptries .	23	33
Range of accommodation .	10	

Fig. 134 shows diagrammatically the alterations which occur in the structures at the anterior of the eye during accommodation.

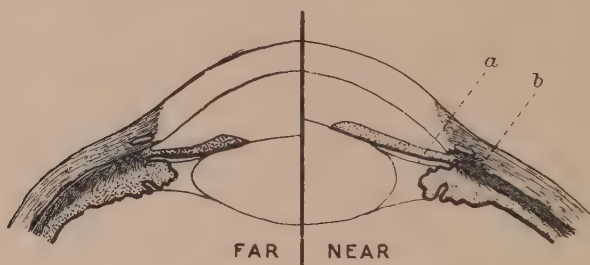


FIG. 134.—Diagram showing mechanism of accommodation.
(After Helmholtz and Foster.)

a, suspensory ligament; *b*, radial fibres of ciliary muscle.

THE MECHANISM OF ACCOMMODATION.—The muscles in the ciliary bodies consist of a superficial radial set and a deeper bundle of circular fibres. The radial set originate in the ligamentum pectinatum, which forms part of the root of the iris at the cornea-scleral junction, and are inserted into the chorioid near the base of the ciliary bodies. When these fibres contract they draw the bases of the ciliary bodies forwards and inwards towards the apex of the cornea. The more deeply placed circular fibres on contraction cause the apices of the ciliary processes to approach the optical axis of the eye. Their combined action, therefore, is to narrow the ring produced by the edges of the ciliary processes and to cause that ring to move forward slightly. Opposing this action there is the tension in the chorioid which is set up by the intra-ocular pressure. In consequence, there is antagonism between the tension of the chorioid, which is tending to make the ring produced by the edges of the ciliary processes larger, and the tension in the muscles which is tending to

produce a narrowing. Suppose, then, the muscles to be entirely relaxed. The tension in the chorioid is unopposed. The ring formed by the ciliary processes tends to widen, and tension is therefore set up in the suspensory ligaments. These in their turn pull on the crystalline lens and reduce its curvature. If, on the other hand, the ciliary muscles are contracted, they draw the ciliary processes together, remove altogether the tension on the suspensory ligaments and permit the crystalline lens to resume its natural curved form. If the muscles are set to the intermediate tension the suspensory ligaments are also sustaining an intermediate tension, and the crystalline lens therefore assumes a shape which is intermediate between its curved condition and the flattened condition it assumes when the suspensory ligaments of the lens pull on it with the maximum tension. This theory with variations in detail is at the present time almost universally accepted.

The student should be careful to remember that the radial and circular ciliary muscles act in co-operation. Both are innervated by the third nerve, and both, when they contract, tend to accommodate the eye for near objects.

THE AMPLITUDE OF ACCOMMODATION.—The amplitude of accommodation varies with the age of the individual, as the following table shows:—

Age in years.	Accommodation in dioptries.
10	13·8
15	12·6
20	11·5
25	10·2
30	8·9
35	7·3
40	5·8
45	3·7
50	2·0
55	1·3
60	1·1

The decrease in the amplitude of accommodation as age advances is due to the hardening of the crystalline lens which reduces its elasticity and therefore prevents its return to the more curved shape which was normal to it in early life.

The amplitude of accommodation is best measured by placing a spectacle frame in front of the patient's eyes. Negative lenses of increasing power are then tried in order to ascertain carefully the strongest negative lens which just permits clear vision of test

designs placed at a fixed distance from the observer. Having noted the power in dioptries of this lens, positive lenses of increasing power are now tried instead, and the most powerful positive lens thus found which will still permit clear vision of the same designs at the same distance. The difference in the powers of these two lenses stated in dioptries is the range of accommodation of the eye in question. For example, an individual of forty-two years of age was tested. The test designs were placed at a metre distance from him. The strongest negative lens through which he could see clearly was $-4.5D$. The strongest positive lens which he could tolerate with the designs still at 1 metre distance was $+1.5D$. It was concluded, therefore, that his range of accommodation was $6D$. From the table it will be seen that an individual of forty-two has a range between 5.8 and 3.7 . In other words, this individual had a greater range than is normal for men of his age.

A marked diminution in the amplitude of accommodation for a patient of a given age is an important indication that there is some serious error in the refracting system of the eye. The commonest of these is spasm of the ciliary muscles. That is, the muscles suffer from a variety of cramp and they never properly relax when distant objects are being viewed. The condition is almost always accompanied by headache. The correct treatment is to give the patient a holiday, and treat the eyes with atropine, which paralyses the ciliary muscles and thus abolishes the tension in them. At the same time the oculist should prescribe spectacles to correct any abnormalities in the refraction of the eyes.

EFFECTS OF DRUGS.—Atropine has already been alluded to as producing paralysis in the ciliary muscles. Homatropine and scopolamine produce a similar effect. One of these drugs placed either as a fluid or as a minute tabloid in the fold of the lower lid, diffuses slowly from there to the ciliary muscles and causes their complete relaxation. On the contrary, contraction of the ciliary muscles is produced by the drugs pilocarpine and physostigmine (eserine).

SECTION V

THE REFRACTION OF THE EYE.—The focal length of the lens system of the eye is approximately two-thirds of an inch. That is, it behaves very like the two-thirds inch microscope objective which is familiar to medical students.

For just the same reasons that microscope objectives suffer from imperfections, so also does the lens system of the eye; that is, even the most perfect sight does not enable the image of a distant

point of light (*e.g.* a star) to form an absolutely sharp image on the retina. There are two reasons for this. One is because light consists of waves in the ether. These waves cannot be made to sweep together to a single point. A phenomenon called diffraction causes this point to be a blur even with a most perfect lens. The second reason is that all lenses suffer from some degree of error. In the case of the eye chromatic error, as it is called, is probably the most serious. Instead of all the waves of different colour arriving at one and the same focus, they arrive at different foci, those corresponding to blue light arriving at a focus closer to the lens system than those from red light. The intermediate colours hold an intermediate position.

There are other errors, the amounts of which can be measured. Consequently the image produced by the lens system of the eye on the retina does not consist of a sharply defined bright point of light when, for example, a distant star is looked at. It consists of a blur the size of which is accurately known. But those of us with good vision know that the defining power of the eye is of an extremely high order. These sense organs are peculiar for the fineness of the detail which they are able to render to consciousness. How do we explain this?

We shall see later that the retina consists of a mosaic of an enormous number of separate sensitive cells. These cells have obviously certain finite dimensions. So long as the blur produced by the lens system of the eye is not so gross that a large number of these sensory elements are simultaneously affected, there will be no noticeable impairment in vision. Let us examine this state of affairs a little more in detail. Suppose we are examining two stars which are situated a considerable distance apart in space, but which appear to our eyes to be very close together. The images of both these stars are blurs. If by an optical device we cause the images of these stars to approach closer and closer to one another, the blurs also approach until a certain point is reached at which we find it impossible to say whether the blur is produced by one star or by two. That is, there is no shadow running down the centre of the combined blur to indicate that there are really two blurs present and not one only. Now, if the fineness of the retina is such that when these blurs are very nearly merging the centre of one corresponds to one sensory retinal element (call this Cone A) while the centre of the shadow between them corresponds to the one next it to the right (Cone B), and the centre of the second blur corresponds to the one next to the right again (Cone C), then an efficient arrangement would have been obtained, because if the cones were made finer no further information would be obtainable. On the contrary, if

the blurs were made finer, again no additional information would be available. In other words, the conditions present are the most suitable, namely, that there shall be between two cones stimulated by the centres of the blurs an intermediate Cone B, which records the existence of a shadow. Careful experiment shows that this is precisely the state of affairs in the human eye.

ABNORMAL REFRACTION OF THE EYE (AMETROPIA).—

Before describing the different types of abnormality met with, a description will be given of the methods of diagnosis. The first thing to determine is how the patient's vision compares with that of normal persons. He is placed at a standard distance of 6 metres from a chart of test letters. The letters composing this subtend definite angles at his eye. The bottom line but one, for example, consists of letters the black lines composing which subtend 1 minute of arc at his eye when he is 6 metres away. A person with normal sight can read this line correctly at this distance. The line immediately above should be read by a normal-sighted person at a distance of 9 metres, but since the patient is situated 6 metres away he will have six-ninths normal vision if he is only just able to read it. The line above that will represent six-twelfths vision, and so on, the top line representing six-thirty-sixths vision. People with very grave abnormality of vision may not even be able to recognise this, and in that event the distance must be reduced until they can read it. Suppose a man can read the top line at 1 metre distance, his vision would be said to be one-thirty-sixth.

THE STENOPÆIC DISC.—A spectacle frame is placed in front of the eyes. In one lens frame is placed an opaque screen, in the other is put a metal disc which has drilled in the centre of it a hole of about one-third millimetre diameter. The disc and the edges of the hole are very carefully blackened to avoid reflections. At the same time the illumination on the test type is increased approximately ten times because the quantity of light now entering the eye is roughly one-tenth what it was before. If a marked improvement in visual acuity is effected, proof is at once obtained that the defect lies in the refracting system of the eye, and that the retina itself is not at fault. On the contrary, if there is no improvement or the improvement is trifling, the probability is that the defect lies in the retina, or, possibly, in both retina and refracting apparatus.

THE MIRROR TEST.—The next test to be applied is known as the mirror test. It has the very great advantage of being

entirely independent of the patient. Thus, a baby or a dumb man can be tested as easily as a normal adult. The method consists in directing into the eye by means of a plain mirror a beam of light from a light-source which is placed just to one side of the patient's head. The doctor looks through a small hole which has been made in the centre of the mirror. When the beam of light is directed into the patient's eye the doctor sees a pink reflected beam coming back to him through his patient's pupil, because the rays of light illuminate a portion of the retina, and this now acts as a source of light, and rays proceed from it to leave the eye at the pupil. Some of these reach the doctor's eye through the aperture in the mirror. As the mirror is tilted slightly upwards and slightly downwards the pink emergent beam appears to move. If it appears to descend when the mirror directs the beam of light downwards, the movement is described as being *with* the mirror. The rule is to place positive lenses in the spectacle frame in front of the patient's eye until a lens of such value is found that the emergent beam appears to remain stationary and independent of the mirror's movements. On the contrary, if the emergent pink beam appears to ascend when the beam cast by the mirror is caused by the doctor to descend and *vice versa*, this is spoken of as movement *against* the mirror, and negative lenses of various powers should be placed in front of the patient's eye until, by trial and error, one is found which causes no movement of the emergent beam to occur. Having tested his patient with the mirror moved vertically up and down, and having ascertained the best correction, the doctor now proceeds to test him further, moving the mirror in such a way that the beam moves from right to left because, as will appear later, the correction in axes at right angles may be different. The doctor carefully notes: (1) the distance between himself and his patient; (2) the power of the lens which effects the correction, and whether it be positive or negative. He has found the lens which will correct his patient's vision for the distance which separates him from his patient.

Suppose, for the sake of argument, that they are a metre apart, and suppose that he finds his patient's vision requires a $+6D$ lens. Then, he knows that a person with normal sight, whose vision is focussed at infinity, would require a $+1D$ lens to cause it to focus at 1 metre distance. The lens he should order for his patient for use for distant vision would therefore be $+5D$. Alternatively, suppose he finds another patient to require a $-3.5D$ lens; then a $-4.5D$ lens would be the correct one to use for distant vision.

THE USE OF ATROPINE.—It is advantageous and greatly increases the accuracy of the mirror test, although it is not absolutely essential, if the patient's accommodation be paralysed before the test by means of atropine or homatropine. The use of these drugs facilitates the tests by greatly enlarging the diameter of the pupil.

Having in this way ascertained the lenses which correct the patient's vision, the doctor places these lenses in spectacles and tests his patient once more with the test type. The improvement is carefully noted and one or two trials are made to see if alternative lenses near these in value give improved results.

The following day, when the effects of the atropine have passed off, the doctor tries these spectacle lenses once more before finally prescribing them for his patient's use.

HYPERMETROPIA.—If positive lenses above 1D were required in both meridians the patient was hypermetropic, or long-sighted. This is the normal state of affairs in childhood because, at birth, the eyeball is too short in comparison with the lens system with which it is provided. As manhood is reached the eyeball grows until it is precisely suited to its lens system. In a certain number of individuals this growth does not take place

and the individual therefore remains long-sighted for the rest of his life. In consequence, the rays from distant objects are brought to a focus behind the retina (see Fig. 135, *B*) and a certain amount of accommodation has all the time to be used in order to focus these correctly on the retina. It follows from this that less accommodation is left for focussing near objects and, since near objects are badly seen, the individual is referred to as being long-sighted. In point of fact he has no better long sight than that of a normal person.



FIG. 135.—Diagram of course taken by parallel rays on entering the eye. (From Starling's *Principles of Physiology*.)

A, an emmetropic, i.e. normal-sighted; *B*, a hypermetropic; and *C*, a myopic eye.

MYOPIA.—Alternatively, suppose the patient required negative lenses. This is a clear indication of the opposite

condition, myopia, or short sight. As a rule this is due to the eyeball being too long in comparison with the lens system which it contains. Such a state of affairs develops in youth, particularly at the school age, when rapid bodily growth is taking place and nutrition is usually defective. The sclera, being ill-nourished, does not withstand the constant intra-ocular pressure to which it is subjected. It gives way, the eyeball in consequence lengthens, further thinning of the sclera takes place so that it is still less able to withstand the intra-ocular pressure, and, as a result, things rapidly progress from bad to worse. The detection of myopia in the early stages is essential. The correct treatment is to attend carefully to the health and nutrition of the children affected, to prescribe glasses which the mirror test shows to be necessary, and carefully to guard against conditions such as working or reading books by artificial light, which are likely to set up eye strain. If detected and treated early, myopia may disappear.

ASTIGMATISM is the condition where one axis of the lens system of the eye refracts to a greater or less degree than the axis at right angles. There are, in consequence, two different foci, one for vertical lines and a different one for horizontal lines, as is shown in Fig. 136. It will be seen at once that a variety of classes

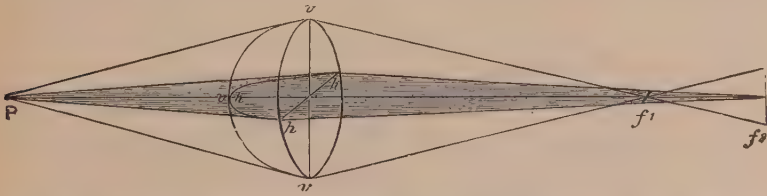


FIG. 136.—Diagram to show the course of rays in an astigmatic eye. (Waller.)
(From Starling's *Principles of Physiology*.)

The rays (from P) in the vertical meridian, *v v*, come to a focus sooner than those in the horizontal meridian, *h h*.

of astigmatism may be met with. The patient may be hypermetropic in both axes, more so in one than the other. Or he may be hypermetropic in one axis and normal in the other. He may be hypermetropic in one axis and myopic in the other. He may be normal in one axis and myopic in the other. Or he may be myopic in both to different degrees. But, further, these axes, which are always at right angles, may be situated in any meridian. Astigmatism is detected and treated in a precisely similar manner to long or short sight. Cylindrical spectacle lenses of the correct strength are used in order to cause the foci of the two rays at right angles to become identical and to correspond to the retina.

SECTION VI

HISTOLOGY OF THE RETINA.—The delicate retina lies, as we have said, immediately inside the vascular chorioid. Its internal surface is in contact with the hyaloid membrane of the vitreous body. It is thus supported on both sides. Embryologically it may be regarded as consisting of two layers, a pigmented outer layer and an inner nervous layer. Histologically,

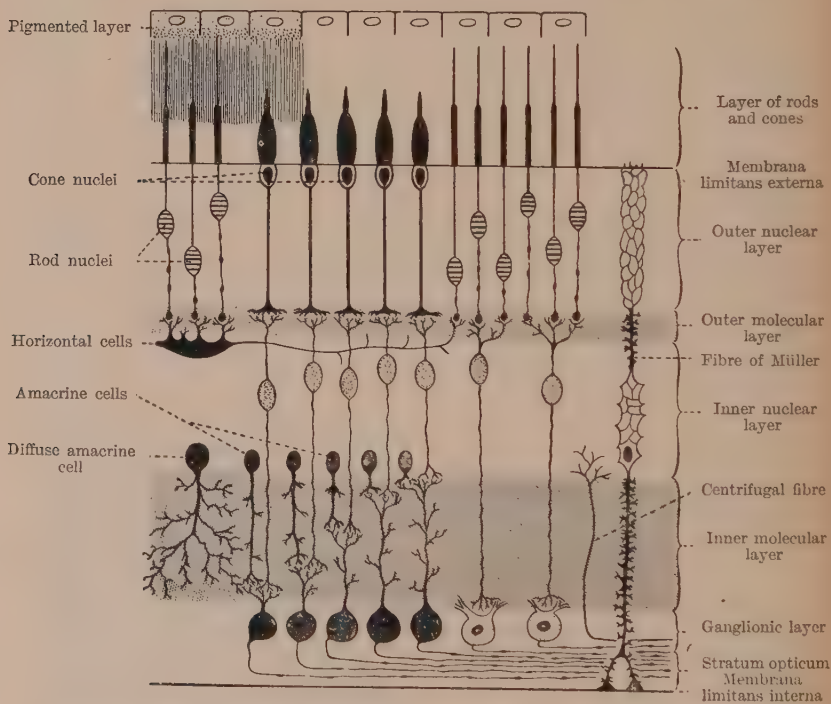


FIG. 137.—Plan of retinal neurones. (After Cajal.) (From Gray's *Anatomy*.)

however, the fully developed retina consists of eight layers, as shown in Fig. 137. These, from without inwards, are:—

(1) The stratum pigmenti, a single layer of hexagonal epithelial cells containing numerous granules. The bases of the cells are firmly attached to the chorioid. Fine pigment-containing processes protrude from the cells between the limbs of the rods.

(2) The layer of rods and cones. These protrude through the external limiting membrane. Their processes are thus external to the membrane, but their nuclei lie internal to it. Both are

striated, the cones coarsely, the rods somewhat more finely. When hardening for histological purposes they frequently break up into discs.

The successive layers will be best remembered if the student bears in mind that two essential nervous elements are represented in the retina. In just the same way that between the sensory end-organ in the skin and the cerebral cortex to which the sensory impulses are finally conducted, there are three orders of neurones (the first conveying the impulses from the sensory end-organ into the spinal cord, the second conveying the impulses from the cord to the optic thalamus almost always crossing on the way, the third conveying the impulses from the optic thalamus to the cerebral cortex), so in the retina the sensations originating in the rods or cones as a result of the incidence of light are conveyed through these three orders of neurones. The first order neurones are situated in the retina itself; so also are the nerve cells of the second order neurones. The optic nerve, composed of fibres which are the axons of these second order neurone cells, conveys these impulses to the third order relays, the cells of which are found, as we shall see, in the external geniculate body. It is because of the situation of these first and second order neurones in the retina in close association with the rods and cones that the retina itself is correctly referred to as being part of the central nervous system.

(3) Immediately inside the rod and cone layer are the nuclei and cell bodies of the rods and cones.

(4) Inside again we find the outer molecular layer which consists of the anastomosing dendritic endings of the rod and cone cells, and the first order relay cells.

(5) The inner nuclear layer is formed of the cell bodies of these first order relay bipolar cells.

(6) The inner molecular layer consists of the dendritic anastomoses between the bipolars and the second order relay fibres.

(7) The ganglion cell layer consists of the large cell bodies of the second order relay fibres.

(8) The layer of nerve-fibres is formed of the axons given off by the ganglion cells, which, sweeping over the inner surface of the retina towards the papilla and the optic nerve, turn abruptly through a right angle to emerge from the eyeball as the optic nerve.

THE OPTIC NERVE.—Having passed through the interlacing grid formed of bundles of white fibres which is a continuation of the scleral coat and is known as the lamina cribrosa, the fibres of the optic nerve separate and their medullary sheaths for the first time make their appearance. For the rest of the course the fibres of the optic nerve are medullated. Where

the papilla of the optic nerve is found and the fibres of the optic nerve are sweeping towards their exit, the sensory elements of the retina are absent. In consequence this part of the retina is called the blind spot. Its existence may be readily demonstrated if the student will make use of Fig. 138. The

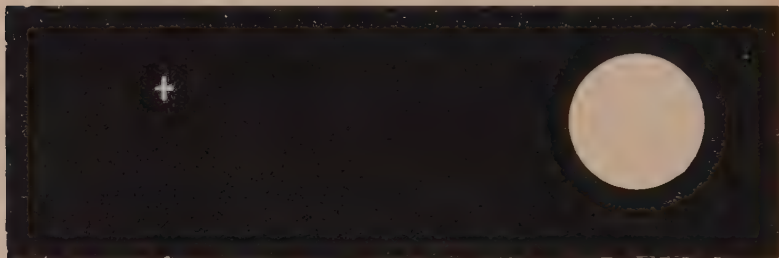


FIG. 138.—Blind spot test. (From Starling's *Principles of Physiology*.)

left eye being closed, the right eye gazes steadily at the cross. The eye is now moved a little towards or away from the book. When the distance is correct (somewhere about 8 inches) it will be seen that the white circle disappears—the image of the white circle is falling on the blind spot. A moment's consideration will show that the blind spot, and therefore the papilla of the optic nerve, is situated to the nasal side of the optical axis of the eye.

THE FOVEA.—Slightly to the temporal side of this axis is observed a shallow pit in the retina. Further, this pit and its surroundings are stained somewhat yellow in colour. Careful histological examination reveals the fact that this little pit, or fovea as it is called, is a structure which shows considerable differences from that of the rest of the retina. In the first place there are no rods. Secondly, the cones are extremely numerous, are elongated, and are so tightly packed together that on section they are seen to be hexagonal in shape. Whereas in most parts of the retina several rods may communicate with one first order bipolar cell and several bipolar cells may communicate with one ganglion cell, so that in fact the impulses originating from many rods are concentrated in one nerve-fibre, in the fovea, on the contrary, each cone has its own first order relay and its own ganglion cell. The ganglion cells belonging individually to each cone are not situated internal to them as they are in the rest of the retina, but are displaced a considerable distance to right or left, above or below. The pit of the fovea is, in fact, produced by this absence of ganglion cells from the fovea

itself and their heaping up at the pit's margin. The object of this arrangement is clear. The histological structures of the eye are very transparent to light, but the ganglion cell bodies offer some interference to the light rays which pass through them on their way to the rods and cones. To avoid this interference with the rays which are destined to reach the tightly packed cones of the fovea, the ganglion cells are displaced to one side in such a way that the nerve paths still retain their correct integrity and distribution, while the light rays reach the cones with the minimum amount of disturbance. It is because of this curious histological arrangement, and because of the close arrangement of the cones, and because the fovea is situated at the best position with regard to the optical system of the eye, that this part of the retina possesses the extremely high acuteness for detail which experiment and our everyday experiences confirm it to possess.

SECTION VII

CHANGES IN THE RETINA ON EXPOSURE TO LIGHT.—

These changes may be classified as structural, physical, chemical, and physiological.

Two structural changes occur, as is clearly seen in Fig. 139. If B, representing retina that has been kept in the dark, be

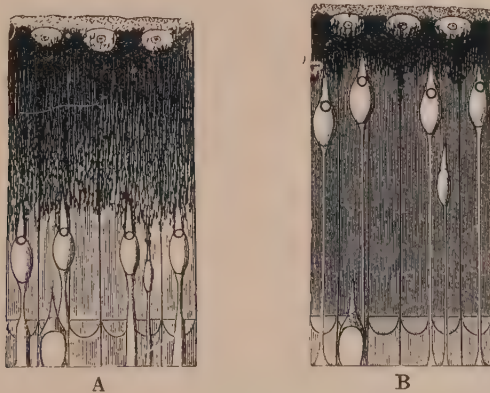


FIG. 139.—Sections of the frog's retina. (From Starling's *Principles of Physiology*.)

A, after exposure to light; B, kept in the dark. (Engelmann.)

contrasted with A, representing retina exposed to the light, it will be seen that the cones which have elongated themselves in the dark until they nearly reach the layer of pigment cells, have strongly retracted themselves so as almost to reach the

external limiting membrane on exposure to light. On the contrary, the processes of the pigment cells which are close to these cells in the dark, have extended a long way towards the external limiting membrane on exposure to light. It is interesting to find that electrical stimulation of the optic nerve will bring about movement of the cones but not of the pigment; also that the incidence of light on one eye will bring about movement in the cones of the other.

The principal physical change is an electric variation which shows itself if non-polarisable electrodes are placed one against the retina and the other against the optic nerve and these are connected to a delicate galvanometer. They are due to the passage of the nerve impulses along the optic nerve-fibres. Adrian has recently used this electric variation for investigating the properties of eels' retinae.

Two chemical changes are described as occurring. In the first place it is said that the retina on exposure to light becomes more acid. The second change is a bleaching of the purple pigment or rhodopsin which is found principally associated with the rods, and is, therefore, practically speaking, absent from the fovea, where cones alone are found. The photo-chemistry of this "visual purple" has been thoroughly investigated in recent years by Hecht and his co-workers. Not only has this observer proved the long suspected connection between the bleaching of visual purple by light, and the type of twilight vision which is a function of the rods, but he has proved a number of important chemical and optical points with regard to this pigment; so that we are justified in making some such statement as the following:—

A retina not previously exposed to light for some time contains a large quantity of visual purple. This is situated near the outer ends of the rods; that is to say, between the pigment cell layer and the external limiting membrane. When light of all wave-lengths falls on the retina a portion of this light energy is absorbed by the visual purple, red rays and violet rays only a little, but green rays to a very marked degree. In obedience to Draper's law, a large and important photo-chemical change is brought about by these green rays, and a part of the visual purple is broken up into two constituents, both of which being colourless are invisible. One of these stimulates the rods and causes them to send up a response along the optic nerve. But the photo-chemical change is a reversible one, and directly the light is removed these two products in the presence of oxygen and in contact with the living pigment cells, are resynthesised to visual purple once more. Our experiment agrees with the

mathematical analysis in showing that the concentration of the breakdown products present at any time bears a certain proportion to the intensity of the light incident on the retina. In other words, the rods are enabled in this way to measure the light intensity. There is ample evidence in favour of this view. Night blindness, for example, is met with at the fovea since there are no rods there. It is also met with in all parts of the retina, whether there are rods there or not, in cases of severe jaundice, the reason being that the bile salts circulating in the blood dissolve away the visual purple from the retina and thus prevent the twilight vision apparatus from operating properly.

THE CENTRAL CONNECTIONS OF THE RETINA.—After the optic nerves have left the eyeballs they converge on one another and meet at the chiasma. They then diverge again, and, being now called optic tracts, they pass through the external geniculate body of the optic thalamus; here they relay at the third order relay cells, the axons of which convey the impulses to the occipital and calcarine cerebral cortex. Further details of this path will be found in the section on Vision in Chapter X on the Central Nervous System. See specially Fig. 102, page 234.

THE VISUAL FIELDS.—Our experiences lead us to think that visual acuity decreases as the image of an external object passes away from the fovea of the retina towards its periphery. Experiment justifies these ideas. It also shows that colours are imperfectly recognised by the peripheral parts of the retina. In consequence of this, if, for the sake of argument, a piece of red paper is brought into the field of vision at its extreme periphery the paper is recognised as being there but at first its colour cannot even be guessed at. As it is continuously moved in towards the fovea a stage is reached at which it suddenly appears yellow, and

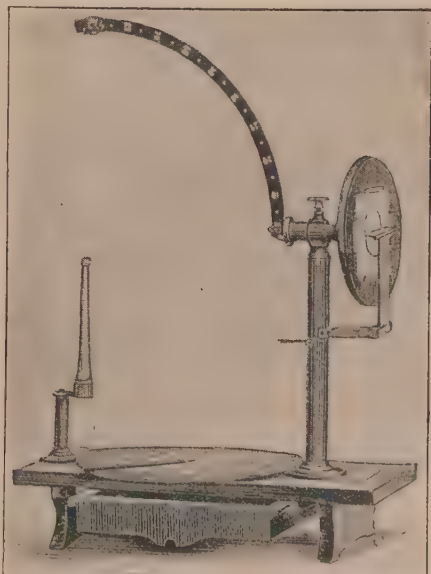


FIG. 140.—Priestley Smith's perimeter.
(From Starling's *Principles of Physiology*.)

it will remain yellow until the angle it makes with the visual axis is probably reduced to about 30° when its correct tint is suddenly recognised. In mapping out the visual fields an instrument called a perimeter is made use of. A very rough one is diagrammatically illustrated in Fig. 140. A perimetric chart for the



FIG. 141.—Perimetric chart for right eye, showing fields for white, blue (and yellow), red, and green. (After Howell.)

right eye, showing the sizes of the fields for the different colours, is given in Fig. 141.

Another interesting fact with regard to the visual field is that it extends considerably beyond the right angle when brow and cheeks do not obstruct it. Thus, a man whose visual axes are directed straight in front of him can observe movements occurring at a considerable angle behind him. Experiment shows that this angle is roughly 14° beyond the right angle.

It is not difficult to see how these rays enter the eye (Fig. 142)

In pathological conditions the visual fields are frequently affected. Thus, if one eye is blind and the other normal, without obvious cause, injury or disease has probably involved the retina or the optic nerve of the blind eye. If blindness involves the right halves of both retinae, it can be explained by a lesion in one of the optic tracts. If blindness is limited to a segment of the retina it is probably one of the retinal vessels which has been obstructed. If the periphery of the retina is affected and the centre is intact, it may be due to an excessive intra-ocular pressure, or a defective blood supply, or the presence of poisons in the blood. On the contrary, if the periphery is normal, and the centre of the retina blind, the cause is probably poisoning by tobacco or alcohol, or a combination of the two.

In addition to total blindness involving a particular restricted area, the condition colour blindness may be met with. The detection of this is important because of the use of coloured lights as signals on the railways and at sea. The tests for colour

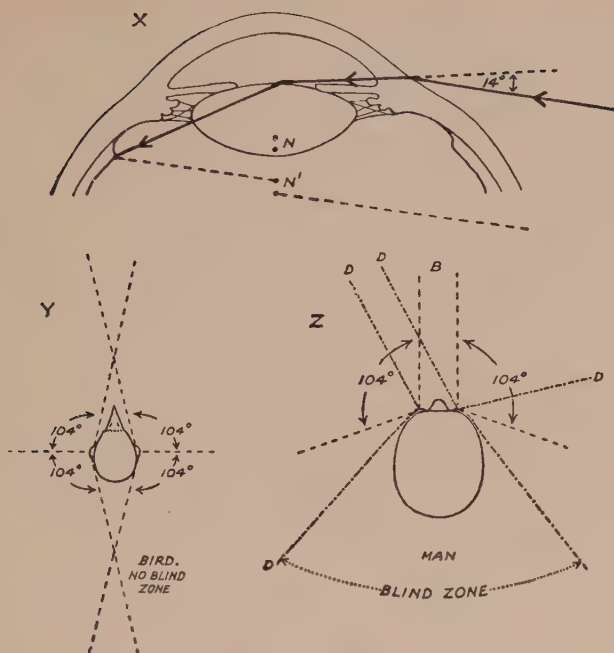


FIG. 142.—Diagram showing how rays from the extreme periphery enter the eye and reach the retina. Y shows absence of blind zone in certain birds and animals. Z shows size of blind zone in man. (Hartridge in Starling's *Principles of Physiology*.)

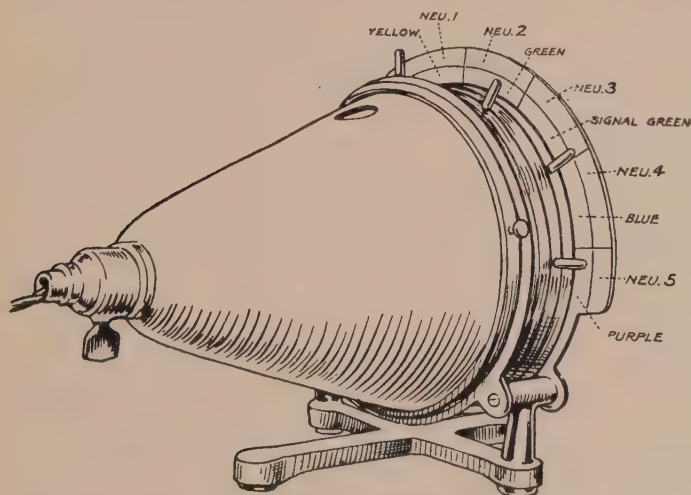


FIG. 143.—The lantern used in practice for the detection of colour blindness. (Edridge Green.) (From Starling's *Principles of Physiology*.)

blindness fall into three categories : those of historic interest only, *e.g.* Holmgren's wool test ; those of use for research purposes, *e.g.* Abney's colour mixture apparatus ; and third, those used by ophthalmologists in order to detect the onset of colour blindness. One of the best tests in the latter class is Edridge Green's lantern (Fig. 143). By means of this apparatus, signal lights of different colours can be presented to the candidate and these can be a very good imitation of the signals which he will be required to detect in his professional capacity. Thus, a red light as seen at a distance of 200 feet on a foggy night can be closely imitated. In all cases he is asked to describe what he sees just as he would have to do to himself if he saw a signal on the railway or at sea.

It is interesting to note that colour blindness, which is far commoner in men than in women, if found in early life is almost always inherited from a colour-blind male ancestor, being handed down to him by unaffected females. Thus, a man may suffer from colour blindness, having inherited it from his grandfather on his mother's side, his mother having normal vision. When found in later life it is almost always due to tobacco poisoning. It should also be noted that colour-blind people are more likely to show their defect in a poor light than in a good one.

SECTION VIII

THE RELATION BETWEEN INTENSITY OF STIMULUS AND SENSATION.—If we arrange suitable apparatus for projecting a bright spectrum, and if we now provide means of altering its intensity from zero right up to the maximum amount, we find that at low intensities the brightest part of the spectrum occurs in the green region. No colours are perceptible. The spectrum appears simply as a grey band gradually rising in intensity until the green region is reached and falling again to zero as we approach the red. On further increasing the intensity of the spectrum, the long and short wave-length ends begin to differ in hue. One end looks bluish, the other end yellowish, and there appears to be a more or less neutral band in between them. An increase in intensity causes the green to separate itself so that it now divides yellow and blue. On further increasing the intensity the other colours gradually emerge until finally all the normal shades of colour in the spectrum are recognised. The brightest colour now, however, is no longer the green but the yellow, or, if the light source which is used to form the spectrum is rich in red rays, the brightest part may even be the orange.

These changes are not difficult to explain. When the spectrum of low intensity fell on the retina it bleached the visual purple to

different degrees according to its intensity and wave-length. The breakdown products of the visual purple stimulated the rods and, in consequence, the twilight vision apparatus which we have described above was stimulated with the result that the spectrum was seen as a colourless band, the brightest colour being that which is most strongly absorbed by the visual purple pigment, namely, the green. On increasing the intensity of the spectrum, however, a point was reached at which an additional mechanism, namely, that provided by the cones, commenced to be stimulated in addition. With each increase in intensity, cone vision improved with the consequent replacement of the rod twilight vision.

The problem that faces us is to account for the properties of cone vision on a basis as satisfactory as that on which we account for rod vision. Unfortunately, this is not possible. All we can do at the present time is to give a description of the most likely manner in which this cone vision functions. The briefer it is and the less detail we attempt to give the better. In the first place it is supposed that instead of one pigment, visual purple, there are three pigments. One of these, since it absorbs green rays, may quite possibly be visual purple; another of them absorbing blue rays may be another pigment, visual yellow, which for many years has been recognised as present in the fovea. The third pigment, which, since it absorbs red rays, must be blue-green in colour, has never, so far as we know, been identified. It is not difficult to see why such a state of affairs exists.

If the function of these pigments is to be sensitive to light, that is, to be bleached white with the production of breakdown products, the surprising thing is not that we have never seen all the pigments, but rather that we have been able to see any of them.

Suppose, then, that red light fell on the retina. It would be absorbed by the hypothetical blue-green pigment, according to Draper's law. Breakdown products would replace the pigment and the quantity of breakdown product present would be notified to consciousness by the cones near the spot on which the light was incident. On the contrary, if the light were green the purple pigments would be bleached and the cones would send up a different type of response. Or if the light were violet, it would be the yellow pigment which was broken down with a different result. So much for the three primary colours.

Suppose, however, the light was yellow. Well, then, we know from the results of colour mixture that this can be synthesised from a mixture of red light and green light. Yellow light falling on the retina would, therefore, partly bleach the blue-green pigment, and would also partly bleach the violet one. Two sets of breakdown products would thus be simultaneously present,

and the amounts of these would be separately assayed by the cones with a corresponding message to the calcarine cortex. In the same way other intermediate colours would be notified. If white light fell on the retina all three pigments would be simultaneously bleached with the production of three kinds of breakdown products and in consequence three separate messages would be sent to the calcarine cortex, for suitable correlation into the recognition of white. This recognition of several substances by the cones should not cause difficulty. Do our tongues not tell us when someone has forgotten to put sugar in our lemonade? Do they not also tell us if in addition to adding sugar, salt has also been inserted? If, then, our taste end-organs can correctly notify us of the amounts of acid, sugar, and salt present in a fluid, is there any outstanding reason why the cones of our retinae should not notify us when three products produced by light action are also present?

SECTION IX

BINOCULAR VISION.—The advantages of binocular vision are that defects in the retinal images of one eye are masked by the impressions received by the other. Thus the blind spots, since they occur in different parts of the visual fields of the two eyes, are not as a rule factors of importance. Further, the fields of the eyes are limited seriously on the nasal side by the prominence of the nose, whereas in the case of both eyes the temporal parts of the fields are almost unobstructed. In the binocular field of vision these unobstructed areas are present at each side.

But, further, binocular vision has the advantage that in certain circumstances it permits stereoscopic vision to be effected, and this provides an extremely correct estimation of distance which greatly assists us in our estimation of size.

In order that there should be binocular vision the following conditions must be complied with: (1) Approximately similar images should be formed on the retinae. We can easily test by experiment what happens when this is not the case. Having placed a stereoscope in front of the eyes take two dissimilar illustrations out of a newspaper or magazine and place them respectively before the eyes. Antagonism between the images will occur. First one will reach consciousness and then the other. Or parts of one may be fitted as mosaics into parts of the other. Only rarely, if at all, will parts of the two be simultaneously presented to consciousness. (2) The external eye-muscles must be able so to adjust the visual axes that the centres of the fields of the two eyes coincide with the images of one and

the same object. When they do not coincide a condition known as diplopia results. If, for example, when we are looking at a distant lamp-post we see not one lamp-post but two, we are suffering from diplopia, a condition which sometimes accompanies poisoning by alcohol. (3) The oblique muscles must also rotate the eyes about their axes until corresponding retinal points occupy corresponding meridians, for otherwise a lamp-post which appears to have one and the same flame may have two different posts inclined to one another at an angle. These adjustments are together called *fixation*. This partly voluntary and partly involuntary act has been considered in Chapter X, Section III.

DEPTH PERCEPTION depends on a number of different factors which as a rule co-operate. Some of these would apply even to a man with only one eye. If the size of an object is known, the distance away may be estimated from the size of the image which is formed on the retina. For example, we can guess how far off a man is. The colour of an object being known, the effect of distance in modifying that colour is used in the estimation of distance. If a tree looks yellow-green, we judge it to be near us. If it looks blue-green or blue we judge that it is some distance away. Partial obstruction of distant objects by nearer ones also assists us, so also do the shadows which some objects cast on others. Perspective sometimes helps us, and the intersection of objects with a horizontal plane gives useful data for reference. Thus, the position of isolated trees in a field may be inferred with some accuracy. If the objects are near to us the degree of accommodation required may give some aid. Lastly, if we are travelling along or if we may make voluntary movements, we can judge of the relative position of objects by the way they move in relationship with one another. Thus, suppose we are travelling in a train and we look out of the window and concentrate our attention on objects a quarter of a mile away. Those in the distance will appear to move in the same direction as ourselves, while those in front appear to move in the opposite direction. Even when we are standing still we may be making small movements which cause us to make judgments by means of parallax.

It is not difficult to prove that, even when every one of these factors is ruled out, people who possess stereoscopic vision can still judge the relative positions of objects. Suppose, for example, we view a uniformly lighted sheet of white paper through an aperture in a screen in such a way that nothing is visible to us whatever but this uniformly lighted sheet. Over the top of the apparatus is mounted a frame, and from this beads may be dropped vertically in different positions. A fine vertical string

is now hung a few inches in front of the sheet of paper. We are asked to state as precisely as possible whether each falling bead lies at the same distance from ourselves as the string or in front of it or behind it. A few tests will suffice to show that our judgments are extremely accurate. This power is due to what is called stereoscopic vision.

Careful experiment shows that this precise judgment is based on the fact that the distances on the right and left retinae between the image of the string and the image of the falling bead are only the same when the distances are the same. On the contrary, suppose that the bead be dropped on the left and in front of the string, then careful measurement shows that to the right eye the apparent distance is a larger one than it is to the left. Alternatively, if the bead falls to the left and behind the string, then to the right eye the distance is smaller than it is to the left. It is this difference between the distances on the two retinae which enables us to make these very precise judgments of distance. This power of stereoscopic vision, which in trained observers is very precise, is made use of in the stereoscopic range-finder.

CHAPTER XIII

HEARING, TASTE AND SMELL

SECTION I

THE PHYSICAL PROPERTIES OF SOUND.—Since sound is a form of wave motion, it has many properties in common with X-rays, light, wireless waves, and the like. It would appear that any material which has the properties of elasticity and mass can conduct sound. Thus, gases, liquids, and solids such as wood, steel, or walls, can be conductors of sound. Like the waves which are observed on the surface of the sea, it does not as a rule form sharp shadows such as light or X-rays do. It is for this reason that it can pass through the bent tubes, for example, of the gramophone or can pass from one room to another through an open door. If sound behaved like light the speaker's throat would have to be a straight tube, and his vocal cords would have to be in a straight line with his mouth and the external auditory meatus of his listeners. Further, the drum of the listener's ear would have to be in a straight line with the speaker's mouth ; otherwise nothing would be audible.

Sources of sound may be divided arbitrarily into two classes : those which produce tones and those which produce noises.

Just as light varies in wave-length and amplitude, so also does sound. On amplitude depends intensity, and on wave-length depends the pitch of the tone. Sounds of short wave-length have a high pitch and those of long wave-length a low pitch. The klaxon and the siren prove this fact conclusively. The limits of pitch for the human ear lie approximately between 30 and 15,000 vibrations per second. So far as the upper limit is concerned, many animals greatly exceed it. For example, notes inaudible to men are readily heard by dogs and cats. Bats carry on communication by means of notes which to most of us are inaudible.

TIMBRE OR QUALITY.—Sounds differ from one another in a third important particular, namely, in timbre or quality. Some

experimenters would describe a fourth quality, "largeness." So far as quality is concerned, recent experimental work has confirmed the conclusion that it depends on the intensity of the harmonies which accompany the fundamental tone. We know at once, for example, the difference between a musical tone produced by a flute and the same tone produced by an oboe or cornet. We also immediately recognise if a singer is representing the vowel "o" or "ah." Analysis of these different sounds shows that the musical tone consists of the fundamental (that is, the tone itself), and, in addition, of a number of overtones which are related mathematically to the fundamental. By suitable means the amplitude of these different overtones may be measured and compared in strength with the fundamental. When this is done for different musical instruments we find that numerous variations occur. A tuning fork just producing an audible hum is accompanied by practically no harmonics at all. The closed organ pipe has a strong fundamental, and, in addition, the first two overtones are just audible. The oboe tone has a hardly perceptible fundamental, while the third and fourth harmonics are extremely strong. In the clarinet tone the eighth, ninth, and tenth harmonics are strongly present with very little fundamental tone. The human voice when producing different vowels is also producing modifications in the strengths of the overtones, the fundamental tone being very weakly represented.

THE EXTERNAL EAR.—The pinna and external auditory meatus form together what is called the external ear. In animals the pinna is a highly developed structure with intrinsic muscles to change it from one shape to another, *e.g.* the pricking of the ears in the dog, external muscles for directing its orifice in different axes relative to the head, and sphincter muscles for varying the size of its lower orifice, thus controlling the intensity of the sound which passes down it to the external auditory meatus. In ourselves the pinna is undergoing retrogression. It is a mere ornament, and will, one supposes, disappear altogether in the course of time. The external auditory meatus in man is about 25 mm. long. It has a slight curve. Its orifice is protected by hairs and by the secretion of a bitter waxy material from modified sebaceous glands. Its external part is formed of cartilage above and below. Its middle part is formed of bone above and cartilage below, while its third part is formed entirely of bone.

THE TYMPANUM.—At the end of the external auditory meatus is the tympanum, which is formed of connective tissue

covered with modified skin on its outer side and by mucous membrane on the inner. It makes a considerable angle with the external auditory meatus and is markedly conical. This conical shape enables the drum to respond to a wide range of pitches because each section of the drum has a different natural period of vibration from every other section. Therefore no particular musical tone can set up more powerful vibrations in the drum than any other tone. This fact, long made use of by Nature, has recently been adapted to the design of the cone loud-speaker.

THE MIDDLE EAR.—The middle ear (Fig. 144), which is an air-containing cavity surrounded on all sides by bone, is lined by mucous membrane. In addition to other structures it contains the chain of three ossicles, some details of which will be given



FIG. 144.—Scheme of ear. (After Landois.)

below. Since it is an air-containing cavity a change in the barometric pressure, or ascent to a high altitude, or descent into a mine, or entry into a compressed-air chamber would cause a different pressure on the outside of the drum from that on the inside of the drum if this air-containing cavity were completely closed. There is, however, an important communication between

the middle ear and the nasal cavity through the Eustachian canal. This canal opens at the posterior extremity of the inferior turbinate bone, but is not permanently open. It is shut by a valve which is relaxed during the act of swallowing, and while it is open it permits the pressure in the middle ear to become the same as that of the external air. Variations in pressure on either side of the drum are thus prevented. It is for this reason that during a descent under water in a caisson or diving suit, and during the subsequent ascent, divers are instructed to swallow periodically. A cold in the head prevents proper equalisation of pressure. The ascent of bacteria into the middle ear occasionally takes place along this canal, and may be followed by very serious consequences.

THE TENSOR TYMPANI.—The drum is put under tension by a special muscle, the tensor tympani, which is innervated by a motor branch from the fifth cranial nerve. Attached to its upper segment is the handle of one of the three ossicles which are found in the middle ear, namely, the malleus. In consequence of this, variations in pressure which accompany the passage of sounds past the head are conveyed down the external auditory meatus to the drum, which they set into vibration, and with it the malleus. These vibrations are communicated to the next bone, the incus, partly by means of the saddle-shaped articulation between the bones, and partly by a projecting spur attached to the body of the malleus which is pressed against the body of the incus. The lower process of the latter has a ball-and-socket joint which holds a rounded projection on the end of the stapes. The footplate of the stapes, which is oval in shape, fits into a corresponding opening in the wall of the internal ear, there being an annular seal between the two which does not prevent the footplate from vibrating, but does prevent the escape of fluid. If, then, vibrations occur in the air outside the head, vibrations are set up in the drum; these are communicated by the malleus to the incus and thus to the stapes, so that the footplate of the stapes sets into vibration the fluid with which the internal ear is filled.

SECTION II

THE INTERNAL EAR.—The petrous portion of the temporal bone contains a series of chambers and tubes which together are known as the labyrinths. The contents of these chambers are used for two entirely separate physiological mechanisms. One belongs to the organ of hearing; the other, as we have already seen, concerns equilibration and the sensations of position and

movements of the head. Inside the bony chambers lie membranous chambers which fit the bony ones very loosely indeed. Between the two is found the fluid perilymph. Inside the membranous chambers is found the endolymph. The parts concerned with equilibration are, as we have already seen, the utricle and saccule, and the three semi-circular canals. Destruction of these disturbs equilibration but does not cause deafness. Here, however, we will only consider the additional important structure, the cochlea, for it is destruction of this which causes deafness. The cochlea

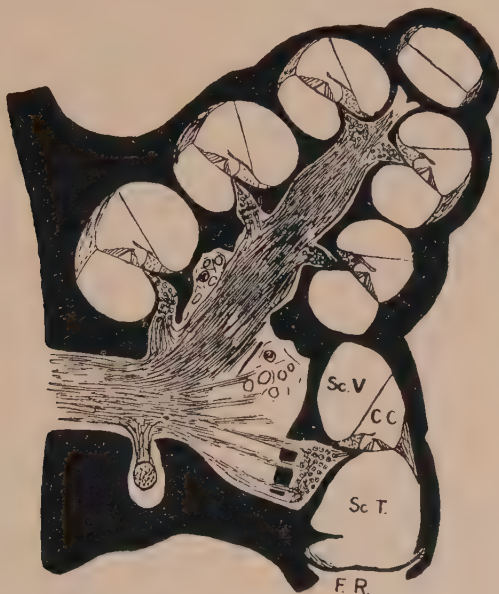


FIG. 145.—Vertical section of the cochlea of the guinea-pig.

Sc.V., scala vestibuli; C.C., canal of the cochlea or scala media; Sc.T., scala tympani; F.R., membrane in fenestra rotunda.

is a spirally wound tube which ascends about a conical mass of bone called the modiolus (Fig. 145). Through clefts in the modiolus fibres of the auditory nerve pass.

THE BASILAR MEMBRANE.—Attached to the surface of the modiolus is the bony spiral lamina which juts out into the spiral cochlear canal, dividing it roughly into two equal parts. Projecting out from the opposite wall of the canal is the stria vascularis. The important basilar membrane stretches across from the tip of the bony spiral lamina to the stria vascularis.

From the cells which lie on the bony spiral lamina runs a second membrane upwards at an angle to be attached to the side wall of the cochlear canal at a point almost vertically above the basilar membrane. This membrane, named after Reissner, divides the upper part of the canal into two portions. The upper one is called the *scala vestibuli*. That lying between Reissner's membrane and the basilar membrane is called the *scala media* or the *ductus cochlearis*, while the canal below the basilar membrane is called the *scala tympani*. The middle canal is filled with endolymph, the other two being filled with perilymph. These three canals, with the other vestibular structures, must now be followed up.

The *scala media*, containing endolymph, connects directly with the interior of the membranous sacculle which, as mentioned above, also contains endolymph. The upper *scala vestibuli*, containing perilymph, connects freely with the fluid surrounding the membranous structures of the vestibules. The footplate of the stapes bone is also in direct communication with this fluid. The lowest canal, the *scala tympani*, which contains perilymph, communicates at the upper end of the spiral with the *scala vestibuli* through a minute opening, the *helicotrema*. The lower end of the *scala tympani* terminates in a small bone-lined chamber, whose only communication is with a round membrane, the external surface of which is in contact with the air in the middle ear.

HOW THE BASILAR MEMBRANE IS SET IN VIBRATION.—

We must now consider in what way vibrations of the footplate of the stapes set up vibrations in these various membranes. When, at a particular instant of time, the footplate is pushed in towards the internal ear a force is applied to the perilymph tending to compress it. But since this is fluid, such compression is impossible. The fluid therefore seeks an outlet. Three possible outlets exist: (1) it may compress the blood-vessels which are nourishing the parts of the mechanism; (2) it may flow up a fine cleft in the temporal bone to a small expansion chamber which lies underneath the *dura mater* of the cranial cavity; or (3) it may flow along the upper canal of the cochlea and, pressing on Reissner's membrane, which is quite thin, communicate its pressure to the endolymph in the *scala media*. This presses in its turn on the basilar membrane and causes it to be displaced downwards, applying pressure in this way to the perilymph in the lower canal. The fluid here, under the increased pressure placed on it, may cause a bulging in the membrane which glazes the round foramen. If, on the contrary,

the footplate be withdrawn, negative pressures are applied where, a moment before, they were positive, and the opposite cycle of events to that described above will therefore take place.

Let us now consider in a little more detail the three possible outlets for the pressure. (1) The blood-vessels are under considerable tension which is being produced in them by the blood-pressure. Unless the pressure exerted by the movements of the stapes were considerable, it is probable that the effects produced on the vessels would be very small. (2) The canal which runs up beneath the dura mater is here long and very narrow, and we know from our observations on the flow of liquid in narrow tubes, that the resistance to rapid movement is very great. (3) Far the easiest of the possible roads is by the displacement of the fine membranes (the basilar and Reissner's).

THE ORGAN OF CORTI.—The basilar membrane has attached to it a series of structures which together form what is called the organ of Corti. To the middle of the upper surface of the basilar membrane are attached the two rods of Corti which,

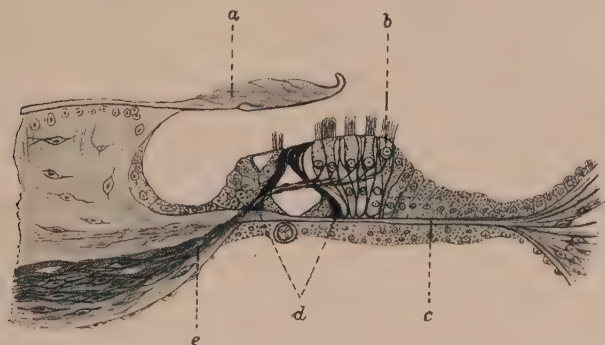


FIG. 146.—Structure of the organ of Corti (diagrammatic).

a, membrana tectoria; *b*, hair-cell; *c*, basilar membrane; *d*, rods of Corti; *e*, cochlear nerve-fibres and (on the left) spiral ganglion.

being inclined to one another, meet at their apices, and form together the arch of Corti. To the side of the arch near the bony spiral lamina is attached a single row of hair-cells which is held in place by further rows of smaller supporting cells. To the outer side of Corti's arch are attached two or three other rows of hair-cells with additional supporting cells. These together lie in such a manner that the fine cilia of the hair-cells all point directly upwards. (See Fig. 146.)

On the underneath side of the basilar membrane are masses of

cells similar in structure to the supporting cells, the object of which, so far as can be judged, is to increase the mass of the whole structure. Attached to the tip of the bony spiral lamina and forming what looks like a roof over the top of the hair-cells is the *membrana tectoria* (Fig. 146). We have already seen the probable manner in which to-and-fro movements of the footplate of the stapes make corresponding up-and-down movements of the basilar membrane, including the structures that we have just been describing.

HOW HAIR-CELLS ARE STIMULATED.—We have now to consider how this up-and-down movement of the structures brings about stimulation of the hair-cells. The most likely of the various hypotheses is the following. Although in some histological sections the *membrana tectoria* appears to be separated from the hairs of the hair-cells, in very carefully made preparations they do not do so. On the contrary, the tips of the hairs actually ramify into and therefore obtain a very firm attachment on the substance of which the *membrana tectoria* is composed. If a downward movement of the basilar membrane takes place, the hair-cells will move downwards too. Then, either the hairs of the hair-cells will have to be stretched or torn, or they will have to pull the *membrana tectoria* in a downward direction also. So far as can be seen, there is nothing to prevent such a downward movement of the *membrana tectoria*. If, a moment later, the basilar membrane rises, the tension in the hairs of the hair-cells will disappear, the hair-cells will rise until they come up against the under surface of the *membrana tectoria*, after which they will apply pressure to it so that the *membrana tectoria* accompanies them in their upward movement. When this upward movement ceases, the basilar membrane first comes to a standstill and then begins to descend; the hairs of the hair-cells will have to pull once more on the *membrana tectoria* because it has first to be brought to rest and then made to travel in a downward direction. Now if traction on the hair-cells acts as a stimulus to them, causing them to impart an impulse to the fibres of the auditory nerve which enters them, then during the time that the basilar membrane is descending, a stimulus will be applied to the corresponding fibres of the auditory nerve. We can thus picture a stimulation of these fibres, which is brought about by the up-and-down movements of the basilar membrane, which in their turn are caused by the in-and-out movements of the footplate of the stapes, which are due to variations in pressure in the air outside the head.

SECTION III

THE ANALYSIS OF SOUNDS.—We have now to consider how it is possible for such an apparatus as this to analyse sounds into their constituent parts, so that, for example, we can recognise what tune is being played and what musical instruments are producing it, or which of our friends is speaking to us, or if a particular noise is due to a motor car.

Careful examination of the different parts of the basilar membrane shows that the length of the basilar membrane and the dimensions of the cellular structures attached to it are quite different at the lower end of the cochlear canal from what they are at the upper. Near the lower end the basilar membrane is short. The cellular structures are small and the attachments of the membrane at the bony spiral lamina and the stria vascularis are extremely strong. Their appearance suggests that the tensions to be withstood must be considerable. Near the upper end of the spiral, however, the basilar membrane is of considerable length, more than three times what it was below, but its attachments to the bony spiral lamina and the stria vascularis appear to be weak. The appearance suggests to our minds a low tension in the basilar membrane fibres. The structures attached to it have a considerable mass, probably ten times or more what they were below. Intermediate portions of the spiral canal show that the parts have dimensions intermediate to those which have been described above. In other words, as we proceed from the lower to the upper end of the canal, we find a lengthening basilar membrane with structures which increase in weight, but apparently decrease in tension in their fibres as we go up. Now the hypothesis which finds nearly universal acceptance at the present time is that the lower parts of the basilar membrane, which are short, lightly loaded, and tightly stretched, are set into sympathetic vibration when notes of high pitch set our ears into vibration; that the long, heavily loaded, and loosely stretched fibres at the upper end of the cochlea vibrate in response to the low tones received by our ears, while all the intermediate musical tones of which we have cognisance set each their own appropriate bank of fibres into vibration. Before going into detail some simple experimental evidence will be given in favour of the "resonance" hypothesis.

BOILER-MAKERS' DEAFNESS.—As the result of listening to sounds of great intensity and high pitch, boiler-makers who have followed their trade for many years suffer from deafness to

high tones in the musical scale. If their cochleas are examined post-mortem it is found that degenerative changes have affected the hair-cells attached to the shorter, lighter, and more strongly tensioned portions of the basilar membrane which are found in the lower part of the cochlear spiral. The experimental destruction of different parts of the basilar membrane in animals leads to deafness of just those notes which would be expected on the above theory. Further, animals subjected to strong musical tones of constant pitch for long periods of time develop what may be thought of as a highly specialised form of boiler-makers' deafness, for localised degenerative changes occur in just those parts of the organ of Corti where they would be expected on the above hypothesis—that is to say, if the tone were a high-pitched one the degeneration would be found in the short fibres; if low-pitched, in the long ones.

Individuals are occasionally found in whom one ear is deaf for a certain limited number of musical tones. This may be easily explained on the above hypothesis as being due to a localised degeneration in a particular part of the organ of Corti.

TONE ANALYSIS.—Having tested the resonance hypothesis and found it to fit in with the facts, let us now consider what precisely happens when musical tones fall on the ear. Suppose that, going to an organ, we press the middle “C” key. We hear the middle “C” tone immediately and we experience the sensation aroused by its vibration so long as we continue to press the key. On removing the finger, the sound apparently stops at once. What is the behaviour of the organ of Corti which causes these experiences? Immediately the musical tone commences, vibrations are set up in the drum of the ear, and these are communicated to the footplate of the stapes and thus to the fluid bathing the basilar membrane. The basilar membrane begins to vibrate, but experiment on models designed to test this point shows that at first a considerable portion may be set into vibration. The short fibres, however, by swinging too quickly, rapidly get out of step with the incoming tone, while the longer fibres by swinging too slowly do the same thing. After three complete vibrations of the sound a very large number of the short and long fibres, by getting out of step, have come to rest, and, relatively speaking, few fibres are now in vibration. The shorter and longer of these in their turn get out of step with the incoming tone, so that after fifteen or twenty vibrations have been received by the ear practically no fibres are vibrating except those whose vibrations are sustained by the musical tone.

GROUP STIMULATION.—It is incorrect to think of one basilar membrane fibre and one fibre only being in vibration as the result of an incident musical tone. The fact is that a hundred or more fibres are in appreciable vibration. One of these has a natural period of vibration which is exactly the same as that of the incoming musical tone. This fibre will suffer the greatest rise and fall, while its neighbours on either side will be suffering a smaller vibration. The more their own period of vibration differs from that of the incoming musical sound, the smaller will be that vibration, so that the fibres fifty-removed on either side from the one in tune will be suffering very small vibrations indeed. Now the hair-cells of a large number of these basilar membrane fibres will be receiving stimulation. Those undergoing the biggest movements presumably send the strongest impulses. But these impulses will clearly be sent up by a very great many more than one set of four hair-cells. Between 100 and 400 hair-cells might be sending up impulses along the nerve-fibres which are distributed to them. But does this mean that more than one musical tone will be heard? Surely not. When we place the point of a needle against our skin and press it, we do not for one moment imagine that we are stimulating one tactile skin sense-organ only. We are probably stimulating a great many. Yet we do not feel many needles but one needle, the reason being that from our infancy until the present day we never felt anything different when a needle pricked us. These same sensory end-organs always have responded together, will always continue to do so, and would immediately notify us that something was wrong if they did not. The same is true of the hair-cells of the organ of Corti. They always have been stimulated in groups, and until something goes wrong, presumably they always will be. This vibration of a limited bank of hair-cells continues therefore so long as the musical tone continues to sound in our ears. Immediately the sound ceases the vibrations in the basilar membrane fibres no longer have incoming energy to assist them and so they quickly die away, as do the vibrations of a gong when we cease to strike it. Since the fibres are immersed in fluid which is no longer being set in motion by the energy of external sounds, the rate of die-away of movement in the basilar membrane fibres is extremely rapid, as is always the case when vibrating structures are immersed in fluid.

THE PERCEPTION OF TWO OR MORE MUSICAL TONES.—

The analysis of a musical chord into its constituent tones can be explained very simply. Each tone on its commencement sets a considerable portion of the basilar membrane into vibration,

The out-of-tune portions die away until, after a very short period of time, only those fibres sustained in vibration by the incoming musical tones are found to be suffering up-and-down movement. Suppose, then, that four musical tones are simultaneously sounded, four different banks of basilar membrane fibres will be set going and will be sustained in vibration. The positions of each of these banks can be at once recognised from the sensations which are received from them up the corresponding fibres of the auditory nerve, and therefore the brain has all the information it requires to identify the particular region of the basilar membrane from which the impulses are being received, and it therefore has the required data for the recognition of the musical tones which are being sounded. The tones produced by different musical instruments can be similarly differentiated because in each the fundamental tone is accompanied by an array of overtones, the intensities of which are typical of the musical instruments in question. In a precisely similar manner we can recognise the different vowels which a singer produces, and from other qualities in his voice can recognise the singer. The consonants concern the manner in which voice tones begin and end, and the same statement is true with regard to the recognition of the different musical instruments which make their tones by percussion, *e.g.* the piano, harpsichord, xylophone, etc.

Some critics have thought that the recognition of noises of different kinds offers difficulties for the above theory, but this is not so. Noises like musical tones differ from one another in the range of pitches which represent them, in the manner in which they commence, and in the manner in which they finish, just as do the musical tones or the voice tones.

SECTION IV

TASTE.—Although the sensations of taste and smell are aroused in different organs, they have a great deal in common. Both are stimulated by chemical substances. In both, chemical substances are dissolved in a fluid medium. Both are employed in the choice of suitable food, both play an important part in rejecting it, if necessary. In both the sensory cells are long spindle-shaped cells, the hair-like ends of which project on the free surfaces.

The tongue is a highly muscular organ covered by mucous membrane. The muscles which run in the three different planes of space are gathered into separate bundles with wide intervening tissue spaces. In this way the muscles are given free play on one another, thus permitting the tongue great freedom of movement.

THE PAPILLÆ.—The mucous membrane is formed into projections or papillæ which differ greatly in size and shape in different parts of the tongue and in the tongues of different animals. There are fine tapering conical, round-topped fungiform, leaf-like foliate (most highly developed in rabbits), flat-topped with a ditch round them (circumvallate), and lastly there are sharp-ended filiform (found in the cat tribe). The sensory taste-buds are found in relationship with the grooves near the bases of all the above except the filiform and conical. The taste-buds themselves consist of collections of taste-cells with supporting cells in between, the whole looking not unlike an onion in transverse section. The tips of the hair-cells are collected together and project a little beyond the external surface of the groove. The placing of the taste-buds in the grooves is clearly to protect them from mechanical injury. In order that the taste-containing substances shall reach these grooves the tongue is sometimes pressed against the hard palate. The nerve-fibres concerned with taste end by arborising among the taste-cells.

THE DIFFERENTIATION OF TASTE.—It is shown by experiment that sweet, sour, bitter, salt, alkaline and, possibly, metallic tastes are the only sensations to which the tongue can respond. Experiment shows, further, that the tongue is not equally sensitive to these tastes at the different parts of its surface. This may be investigated by ascertaining the minimum concentration of the substance in question that may be positively detected with certainty by the different parts of the tongue, or the time taken to recognise one standard solution. By both these methods the back of the tongue is found to be more sensitive to bitter flavours, while sweet and sour sensations are more easily aroused in the tip and sides of the tongue. If a mixture of quinine and sugar be made, or any other pair of radically different taste, and this mixture be tested on a number of different papillæ by painting the mixture on them with a fine paint brush, it will be found that to some the mixture will taste predominantly bitter but to others, predominantly sweet. This seems to point to the different taste-buds having different thresholds for different substances.

THE EFFECTS OF DRUGS.—Drugs painted on the tongue modify considerably the taste sensations. Thus, cocaine diminishes the tactile and pain sensibility of the tongue; bitter sensations then disappear and are followed by sweet and sour. Of all the sensations the one to salt alone remains unaffected.

Another drug, obtained from the leaves of the plant *Gymnema sylvestre*, abolishes the sensations to bitter and sweet but leaves unaltered those to salt and acid; it has no effect on pain and tactile sensibility. It is clear that there is a close similarity between the chemical constitution of substances and the tastes which they arouse. Most alcohols and sugars are sweet, so are all the amino-acids. On the other hand, the metallic derivatives of the alcohols and sugars are bitter, as also are the polypeptides.

Substances which when in solution dissociate to give free H ions cause an acid sensation. Those which liberate hydroxyl ions have an alkaline taste.

THE NERVE SUPPLY TO THE TONGUE.—The hypoglossal, the twelfth cranial nerve, supplies all the muscles of the tongue. The general sensibility of the tongue (touch and pain) travels by the trigeminal or fifth cranial nerve. The taste sensations from the posterior third of the tongue almost certainly travel up by the glosso-pharyngeal or ninth cranial nerve. There is some uncertainty, however, as to the course taken by the taste sensations from the anterior two-thirds of the tongue. They may either travel with the lingual as far as the Gasserian ganglion, then, turning out by its middle division, reach the great superficial petrosal nerve; the fibres may then travel down it to reach the nerve of Jacobson and thus reach the nucleus of the glosso-pharyngeal to go with the fibres from the posterior third of the tongue to the ninth nerve nucleus. Alternatively, passing by the small superficial petrosal, they may reach Jacobson's nerve and then travel as before. Or, leaving the lingual nerve to join the chorda tympani, they could pass with fibres of the facial or seventh cranial nerve, then pass by its branches to the nerve of Jacobson and so to the ninth nerve as before. There seems no doubt that the route is liable to variation in different individuals.

SECTION V

THE SENSE OF SMELL.—As pointed out above, this is a chemical sense like that of taste, but it differs from taste in having the power of projection. That is, whereas to arouse the sense of taste the substances in question must touch the tongue, they can still arouse the sense of smell even when situated a very long way off. Its importance to animals and fishes where sight and hearing are limited must be extremely great.

In ourselves there is evidence that the function is undergoing retrogression. Thus, in dogs and cats, the specialised olfactory epithelium may extend over a considerable surface. In ourselves

this is limited to a small patch at the uppermost extremity of the nasal cavity in a pocket lying above the superior turbinated bone. (See Fig. 147.) So inaccessible does this specialised olfactory epithelium appear in man that the question has been asked, How do odorous substances reach it at all? Experiments have

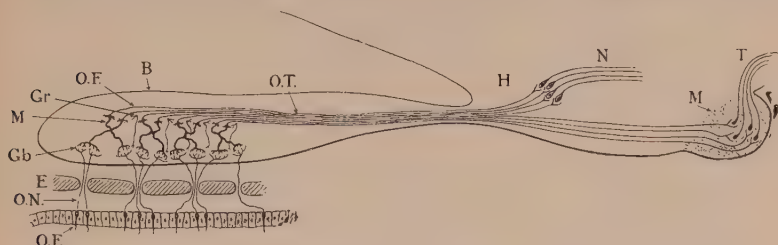


FIG. 147.—Diagram of the olfactory epithelium and of the olfactory bulb and tract.

O.E., olfactory epithelium; O.N., olfactory nerves; E, ethmoid bone; Gb, glomeruli; M, mitral cells; Gr, granule cells; O.F., olfactory fibres, 2nd order; B, olfactory bulb; O.T., olfactory tract; H, hippocampus; N, fibres from hippocampus to cortex; M, corpus mamillaris; T, tractus mamillo-thalamicus.

been performed on the human cranium in two ways. First, the head having been sawn in half and small pieces of alkaline litmus paper placed on different parts of the mucous membrane, the head was fastened together again and an acid vapour aspirated in at the anterior nares and out at the posterior, so as to form a constant current. In a second experimental technique each half of the head was covered by a glass plate and the whole made airtight by means of plasticine. Tobacco smoke was aspirated through and the course taken by the smoke watched through the glass. The evidence obtained from both these experiments is that the air passes from the anterior to the posterior nares along the lower part of the nasal cavity. Most of it remains below the inferior turbinated bone, but a part of the current extends to the middle turbinated bone. Very little flow appears to take place above the middle turbinated bone, and less still to reach the specialised olfactory epithelium. We may now consider how smells are perceived.

DIFFUSION AND CONVECTION.—There are two theories of smelling. One is that the odorous substance diffuses from a rapidly moving current into the upper part of the nasal cavity to reach the olfactory mucous membrane. Against this diffusion hypothesis is the fact that a very large number of odorous substances have large molecules and therefore would probably diffuse very slowly. Another view is that the rapidly moving stream in the lower part of the nasal cavity causes eddies to be set up

in the upper part of the nasal cavity such as are caused in a backwater by a neighbouring stream. Odorous substances are, according to this view, which seems a very plausible one, carried

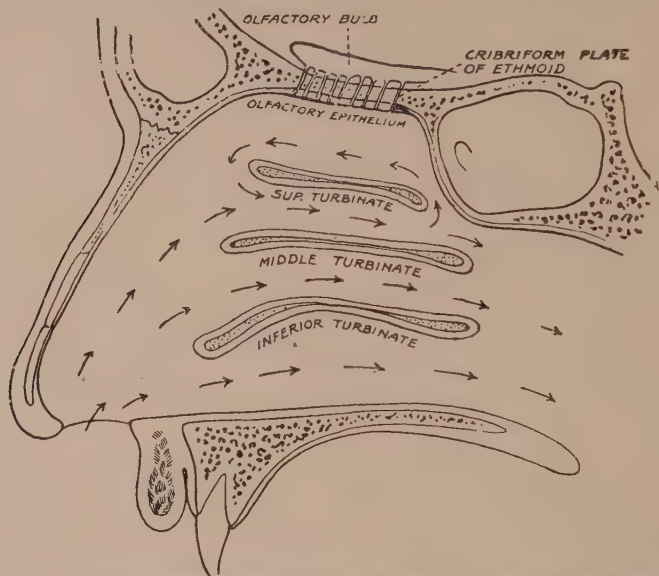


FIG. 148.—Antero-posterior section through the nasal fossæ. The arrows show the direction of the air currents during inspiration. (From Starling's *Principles of Physiology*.)

by these eddies from the surface of the moving stream into the backwater formed by the upper part of the nasal cavity. This is represented in Fig. 148.

THE AMMONIA VAPOUR EXPERIMENT.—The following experiment has been held to prove that the sense of smell is not aroused unless the air be in motion through the nasal cavity. The experimenter sits near a door in a room from which draughts are carefully excluded. He holds in his hand a bottle containing a few c.c. of strong ammonia solution. He unstoppers the bottle and, holding his breath, places the mouth of the bottle close to the anterior nares. He remains motionless. The sting of the ammonia vapour is felt by the skin of his face and by the mucous membrane near the anterior nares, but no smell of ammonia vapour is perceived by him. When he feels short of breath he hastily corks the bottle and, opening the door, moves swiftly into the passage outside, shutting the door behind him. He now makes a powerful inspiration. The resulting smell of ammonia vapour is almost overpowering. The entirely erroneous

conclusion that has been drawn from this experiment is that so long as the air was still no smell of ammonia was aroused, but immediately the air was set in motion stimulation of the olfactory mucous membrane immediately followed. The true explanation of the experimental results is as follows: Ammonia is extremely soluble in fluids. It can also be readily dissolved by the skin and by mucous membrane. When the uncorked bottle of ammonia solution was held near the nose the ammonia vapour diffusing out of the bottle reached the skin and mucous membrane and dissolved there. That this is so is shown by the stinging sensations set up in the skin and mucous membrane near the anterior nares. The ammonia vapour, having saturated the structures near to it, diffused further, reached other surfaces and was absorbed there also, and this process went on so that little by little the area of skin and mucous membrane which had dissolved the ammonia became larger and larger. It would take a very long time indeed for the interior of the nasal cavity to be so saturated with ammonia vapour that the olfactory region was reached. Long before that could happen the stinging sensation would have become so great that the man would want to stop the experiment even if he did not run short of breath. On removing the bottle, however, and making an inspiration, air is swept over the skin and mucous membrane which has taken up the ammonia. The ammonia therefore discharges itself from these structures into the air, and so the air passing in at the anterior nares contains ammonia, some of which reaches the olfactory mucous membrane by means of the eddies which have been described above.

THE DIFFERENTIATION OF SMELLS.—Attempts have been made to divide all the smells with which we are familiar into classes similar to those which we have mentioned above with regard to taste, but these attempts have hitherto ended in disagreement. Three interesting facts may, however, be mentioned: (1) Some otherwise normal individuals are not able to distinguish certain odours, *e.g.* violets, hydrocyanic acid. (2) It is possible to fatigue the nose to one smell and to leave other smells apparently unaffected. (3) It is possible to mix odorous substances together in such a way that they neutralise one another and produce an odourless result. Thus, 4 grammes of iodoform mixed with 200 grammes of balsam of Peru produce a practically odourless mixture. It is said that when these two odours are led separately by tubes one to each nostril and the intensities of the odours are correctly adjusted, a complete neutralisation of the smell may take place.

CHAPTER XIV

SALIVARY AND GASTRIC DIGESTION

SECTION I

THE NATURE OF DIGESTION.—Digestion consists essentially in the splitting up of the molecules of the foodstuffs into a large number of much smaller molecules, which are easily absorbed through the mucous membrane of the digestive tract. Thus the digestion of fat results in the splitting up of the molecule of neutral fat into one molecule of glycerol and three molecules of fatty acid. A single protein molecule is broken up into a very large number, probably a hundred or more, of molecules of amino-acids, while one molecule of starch is subdivided into many molecules of glucose. The process is always one of hydrolysis, and for protein and starch it takes place in a series of stages. Similar changes can be brought about by chemical means, such as boiling with mineral acids, but the digestive fluids achieve their results more rapidly and effectively, at the temperature of the body, by means of certain active agents known as enzymes or ferments.

ENZYMES.—Enzymes are widely distributed in the animal body, and many of the chemical changes which occur in the tissues are due to the activity of these agents. Some remove the NH_2 group from amino-acids, another series is responsible for the various stages in the production of uric acid, and the digestive enzymes are concerned, as described above, with the hydrolysis of the constituents of food.

NATURE OF ENZYMES.—No enzyme has yet been isolated and analysed. Nothing definite therefore is known as to the composition and constitution of these bodies. Solutions containing them have colloidal properties, the molecules of the ferment being relatively large.

SOURCE OF ENZYMES.—Enzymes are products of the activity of cells. Some act intracellularly, as the *zymase* of yeast does.

Others are discharged from the cells in which they are formed, and carry out their function extracellularly. The discharge of such a ferment from the cell usually takes place as the result of a nervous or chemical stimulus, and in the absence of such a stimulus granules of a precursor, or *zymogen*, accumulate in the cell. Generally speaking, this is the behaviour of the digestive ferments, the *zymogen* being converted into the enzyme after its discharge from the cell.

CHARACTERISTICS OF THE ACTION OF ENZYMES.—The action of an enzyme is distinguished by certain definite features.

(1) Each enzyme is *specific*; it will act only on one particular substance, or on one particular group of compounds. For example, three di-saccharides may be found in the digestive tract, sucrose, maltose, and lactose, and each of these is split into mono-saccharides by its own enzyme, these being *invertase*, *maltase*, and *lactase* respectively. Invertase will not act upon maltose, or lactose, and similarly maltase and lactase will each act only upon its own particular sugar. Although *proteolytic enzymes* act only on proteins, it should be noted that the specificity here is rather less limited, since widely dissimilar proteins are alike broken down by the same proteolytic enzymes. A ferment has been compared with a key which will only fit its own lock.

(2) *Water* is necessary. The substrate, or substance acted upon, may be undissolved, while the enzyme is in solution, or the enzyme may be in the form of a precipitate in a solution of the substrate, or both enzyme and substrate may be in solution, but the action of the ferment cannot occur if enzyme and substrate are mixed in the dry state.

(3) *Reversibility*. Most enzymes are reversible. For example, maltase can convert maltose into glucose, but it can also convert glucose into maltose. If the maltose be removed as fast as it is formed, the whole of the glucose will be converted into it and *vice versa*.

(4) *Equilibrium*. If one of the products is not removed, then the reaction will proceed fast at first, but with increasing slowness, until an equilibrium value is reached.

(5) The *rate* at which a ferment will convert a given amount of substrate into its end-products is proportional to the amount of ferment present. A small amount of enzyme acting upon a large quantity of substrate will, subject to the conditions already discussed, act upon equal quantities of substrate in equal times, and will thus gradually accomplish what a larger quantity of ferment would bring about in a much shorter time.

(6) *Temperature* affects the rate of action of enzymes. Like

chemical reactions, it is accelerated, within limits, by a rise of temperature, and slowed by a fall. The optimal temperature for the action of the enzymes of the body is 37° to 40° C., that is, at, or just over, the temperature of the body. The action of an enzyme is arrested by very low temperatures, but the enzyme itself is not destroyed. At or even below the temperature of boiling water, however, all ferments are destroyed.

MODE OF ACTION OF ENZYMES.—Enzymes resemble inorganic catalysts in that they alter the rate of certain chemical reactions without supplying any energy to the process, without forming part of the final products, and without being themselves used up. They may therefore be described as *organic catalysts*.

Probably the first stage in enzymic action consists in either a physical union by *adsorption* between enzyme and substrate, or an actual chemical combination between the two. When the action is hydrolytic, water is also combined with the substrate. An unstable compound is thus formed, which then splits into simpler molecules, and the enzyme is again set free.

SECTION II

SALIVARY DIGESTION.—The activities of the digestive tract are two in number: (1) There is a motor mechanism by means of which the contents of the tract are moved progressively from mouth to œsophagus, stomach, small intestine, and large intestine, and the residues are finally expelled. (2) There is a series of secretory glands which produce the digestive juices met with in the different regions of the tract. The enzymes present in these juices bring about hydrolytic changes in the protein, carbohydrate, and fatty constituents of the various foodstuffs.

On entering the mouth the food is masticated, being directed by the muscular movements of the cheeks, lips, and tongue into position between the opposing teeth, and broken up and formed into a pulpy mass by the vertical, lateral, and antero-posterior movements of the jaws. At the same time saliva is poured into the mouth in considerable quantity, and is intimately mixed with the food by the same movements. After mastication, the food mixed with the saliva is collected into a bolus on the tongue by further movements of the cheeks, lips, and tongue itself, and it is then ready to be swallowed.

Saliva is formed by the three salivary glands, the parotid, sublingual, and submaxillary glands. Each consists of a mass of alveoli or acini bound together by connective tissue; each alveolus is lined by polyhedral cells resting on a basement-membrane,

and opens into a duct. The ducts from the alveoli unite to form larger ducts, and eventually end in one main duct which opens on the surface of the mucous membrane of the mouth.

THE COMPOSITION OF SALIVA.—The saliva which enters the mouth is the mixed secretion of all the salivary glands, together with that of the small buccal glands which are scattered over the mucous membrane of the mouth. It is viscid and colourless, faintly alkaline in reaction, and with a specific gravity which varies from 1002 to 1008. It contains as a rule just over 99 per cent. of water, and less than 1 per cent. of solid constituents. The latter consist of coagulable proteins, mucin, a diastatic enzyme or amylase called *ptyalin*, and inorganic salts, of which calcium carbonate forms a considerable proportion, and which are apt to be deposited as tartar on the teeth. Traces of potassium thiocyanate are indicated when a red colour is produced by the addition of ferric chloride to the saliva.

In man, it is easy to collect separately the saliva from the parotid or submaxillary glands by inserting a small cannula into the parotid duct or into the submaxillary duct (Wharton's duct). It is then found that the submaxillary saliva contains much mucin and little ptyalin, whereas the parotid saliva is free from mucin but is rich in ptyalin. This difference depends upon the fact that two types of cell are found in the salivary glands, one which secretes mucin and is called a mucous cell, and one which secretes ptyalin and other substances and is called a serous cell. In man, the acini of the parotid gland consist entirely of serous cells, and the gland is said to be a serous gland. The submaxillary and sublingual glands in man contain both mucous and serous cells.

THE MUCOUS TYPE.—If a portion of a *mucous* gland which is in the resting condition be teased in 2 per cent. salt solution, the individual cells are seen to be somewhat columnar in shape and to be filled with large granules. In a gland which has been made to secrete profusely, either by means of electrical stimulation or by the administration of pilocarpine, the granules are fewer in

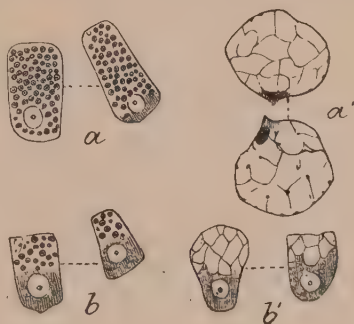


FIG. 149.—Mucous cells from fresh submaxillary gland of the dog. (Langley.) (From Schafer's *Essentials of Histology*.)

a, from a resting or loaded gland; *b*, from a gland which has been secreting for some time; *a'*, *b'*, similar cells which have been treated with dilute acid.

number and are found in the part of the cell which abuts on the lumen of the acinus; and the cell is smaller than that in the resting condition and its nucleus is nearer the lumen (Fig. 149). In the process of secretion, therefore, there has been a discharge of the granules contained in the cell. The material contained in the granules has been called mucinogen.

THE SEROUS TYPE.—The cells of the *serous* type, examined in the same way, are more cubical in shape, with a central nucleus, and in the resting state are diffusely filled with fine zymogen granules, which are supposed to consist of a precursor of ptyalin. As in the mucous cell, the serous cell becomes smaller during activity and the granules are diminished in number, especially towards the base of the cell (Fig. 150). In stained sections of



FIG. 150.—Alveoli of a serous gland. (Langley.) (From Schafer's *Essentials of Histology*.)

A, at rest; B, after a short period of activity; C, after a prolonged period of activity.
In A and B the nuclei are obscured by the granules of zymogen.

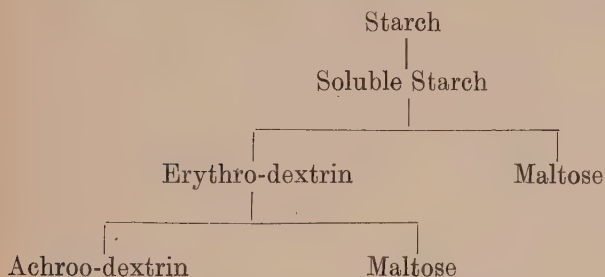
the hardened gland, the cells, even in the resting stage, always appear to contain a relatively greater amount of protoplasm than the mucous cells.

THE FUNCTIONS OF SALIVA.—The saliva not only assists mastication and deglutition by its admixture with the food, but, by keeping the lips and tongue moist, it is of service in those movements which are essential to the function of speech. Further, it dissolves many substances taken into the mouth, and thereby renders them capable of stimulating the gustatory end-organs, and of giving rise to sensations of taste. In addition to these functions saliva has a definite digestive action owing to the presence of ptyalin, which acts upon starch, converting it into dextrin and maltose. Raw starch is only slowly acted upon by saliva, which cannot readily dissolve the capsules of the starch granules. When starch granules are heated in the presence of water, they swell, the capsules are ruptured, and the starch passes into colloidal solution. If a little saliva be mixed with this solution in a test-tube and the mixture kept at 40° C., the slightly

opalescent fluid becomes clear; but if a drop of the clear solution be added to a drop of dilute iodine a blue colour results, as in starch which has undergone no digestive change. Thus the first stage in the process is the formation of *soluble starch*. A little later a drop of the fluid gives a purple colour with iodine, later still a reddish brown, due to erythro-dextrin; finally an "achromic point" is reached. The solution now contains achroo-dextrin and maltose, and gives no coloration with iodine solution.

The digestive power of any particular saliva can be estimated by the time taken to reach the achromic point.

The process may be diagrammatically shown thus:—



THE OPTIMUM H ION CONCENTRATION.—The digestive action of ptyalin on starch is most energetic in a neutral or very faintly acid medium. Hence it is favoured by the addition of a trace of acid to normal alkaline saliva. Like other ferment processes it is arrested by a high temperature. The presence of inorganic salts, especially chlorides, is essential to the activity of ptyalin. Normally these are present in sufficient amount in the saliva.

The food does not remain long enough in the mouth for the ptyalin to convert a large amount of starch into sugar, but salivary digestion continues for a considerable time in the stomach. When a meal is taken, the food, mixed with saliva, forms a compact mass in the stomach, and the hydrochloric acid of the gastric juice penetrates comparatively slowly into this mass. As the acid penetrates it destroys the ptyalin, but, in the interval which elapses before this process is complete, the ptyalin has time to convert a considerable amount of starch into dextrin and maltose. The duration of salivary digestion in the stomach is usually from twenty to forty minutes, but it may be prolonged for an hour or more if the animal remains quiescent after the meal, so that the mass of food is not rapidly broken up by bodily movements.

THE NERVE-SUPPLY OF THE SALIVARY GLANDS.—Each salivary gland receives a double nerve-supply from the central

nervous system. The submaxillary and sublingual glands are supplied by the chorda tympani (Fig. 151), which arises from the

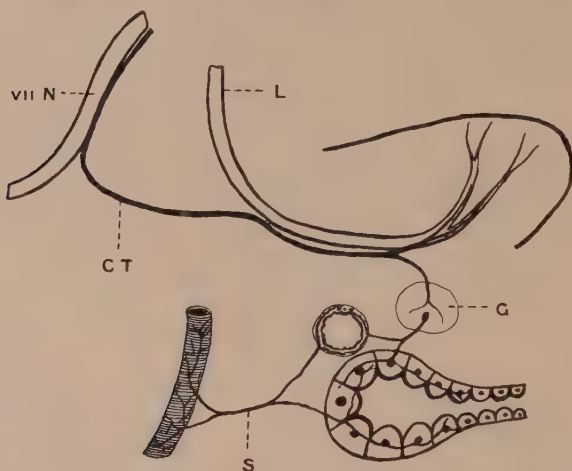


FIG. 151.—Scheme of nerve-supply of submaxillary gland.

VII N, facial nerve; CT, chorda tympani; L, lingual nerve; G, Langley's ganglion
S, sympathetic fibres to the gland.

nervus intermedius. The fibres supplying the parotid gland also originate in the nucleus of the nervus intermedius. All these fibres belong to the cranial autonomic nervous system (p. 291), and a cell-station is found on each nerve-path. From these various ganglia post-ganglionic fibres pass to the respective glands.

All the salivary glands receive a supply from the sympathetic system. In the dog, the pre-ganglionic fibres leave the spinal cord in the white rami communicantes of the first three thoracic nerves, pass through the stellate ganglion, and run in the cervical sympathetic nerve to the superior cervical ganglion, in which they form synapses with nerve-cells. Post-ganglionic fibres from these cells run in the sympathetic plexus on the external carotid artery to the various glands.

FUNCTIONS OF THE NERVES TO THE GLANDS.—The functions of these nerves may be studied in an anæsthetised animal by placing a cannula in the duct of a salivary gland and observing the effect of (1) division of the nerve, and (2) stimulation of its peripheral portion. On stimulation of the peripheral portion of the autonomic nerve with rapidly repeated induction shocks, an abundant flow of viscid saliva takes place, and continues for a few seconds after the cessation of the stimulus. Stimulation of the

peripheral part of the divided cervical sympathetic nerve produces in some animals a scanty flow of saliva, and in others no perceptible flow ; but in all animals prolonged stimulation of this nerve leads to definite histological changes in the gland. Secretion can also be excited by certain drugs, *e.g.* pilocarpine, which stimulate the nerve-endings in the gland.

SECTION III

THE MECHANISM OF SECRETION.—The mechanism by which the secretion of saliva is normally evoked can be most easily studied in a dog provided with a salivary fistula. In such an animal the most potent stimulus to the secretion of saliva is found to be the presence of food or other substances in the mouth. Apparently the food excites the peripheral endings of the afferent fibres of the fifth and ninth nerves in the mucous membrane of the mouth, giving rise to impulses which pass to a salivary centre in the pons, and thence along the efferent nerves to the salivary glands. The secretion is therefore brought about by a reflex mechanism.

All kinds of food are not equally effective in stimulating the reflex mechanism for the production of saliva. Thus dry food causes a more copious flow of parotid saliva than moist food.

The presence of food in the mouth is not the only cause of salivary secretion, since this can be brought about by the sight or smell of food ; secretion excited in this way is known as “psychical” secretion.

The secretion of saliva is also influenced by emotion, being inhibited, for example, in extreme fear. That the secretion of saliva in the normal animal is entirely reflex in origin is shown by the observation that, after section of the chorda tympani and auriculo-temporal nerves, the taking of food is no longer followed by a flow of saliva. So far as is known, the sympathetic nerves to the glands take no part in the normal reflex secretion of saliva, and their function is probably vaso-motor.

CHANGES IN THE BLOOD-SUPPLY DURING SECRETION.—Stimulation of the peripheral portion of the divided chorda tympani causes a flow of saliva. This is accompanied by a dilatation of the arterioles of the submaxillary gland, so that the latter becomes flushed and the amount of blood flowing through it in a given time is greatly increased. Indeed, the flow may be so rapid that the blood leaving the gland is almost arterial in appearance. This vaso-dilatation is an example of a law which holds good throughout the body, that increased functional activity of

any organ is accompanied by an increased blood-supply to that organ; the additional blood-supply provides the organ with the oxygen and nutritive materials which it needs for its activity.

Owing to the relaxation of the arterioles, the blood-pressure in the capillaries of the active submaxillary gland is raised, and it is conceivable that the saliva might be formed by the filtration of water, salts, and other salivary constituents through the capillary wall as a result of the increased pressure. There is abundant evidence, however, that filtration takes no part in the formation of saliva. If one mercury manometer is connected with the duct of the submaxillary gland (Wharton's duct), and another with the carotid artery so as to measure the arterial blood-pressure, and if the chorda tympani is stimulated, the pressure of the saliva which is formed may raise the level of the mercury in the manometer connected with the duct higher than that in the manometer attached to the artery.

These experiments make it clear that the formation of saliva is not brought about by filtration from the capillaries, and it must therefore be due to the "vital" activity of the gland-cells.

THE SECRETORY PROCESS.—The distinguishing features of the secretory process are (1) that the gland-cells manufacture, and discharge into the lumen of the gland, substances which are not present in the blood, and (2) that in forming the secretion the cells carry out work. The process is normally aroused by impulses passing along the nerves to the gland (or, in the case of the pancreas and some other glands, by a chemical messenger or hormone), but the work involved in the act of secretion is effected by the cells themselves, and is determined by them. This fact is confirmed by the histological examination of the cells at various stages of their activity. The cells of the submaxillary gland, for example, during the periods when they are not secreting, form a store of mucinogen granules; when the gland becomes active, these granules are converted into mucin, and the latter is discharged into the duct, together with water and salts, to form saliva.

The amount of material thus discharged from the cells when the secretion is rapid may be so great that the gland actually shrinks, notwithstanding the increased amount of blood contained in its dilated blood-vessels (Fig. 152). Not only the discharge of the secretory granules, but also the transference of water and inorganic salts from the lymph through the gland-cells into the saliva, is effected by the vital activity of these cells. The percentage of inorganic salts in the saliva is much less than that in

the blood-plasma, and consequently the osmotic pressure of the saliva is found to be lower than that of the plasma. If the gland-cells behaved as a semi-permeable membrane, this difference of osmotic pressure would cause fluid to pass from the saliva into the lymph and blood; and the fact that the gland-cells form saliva

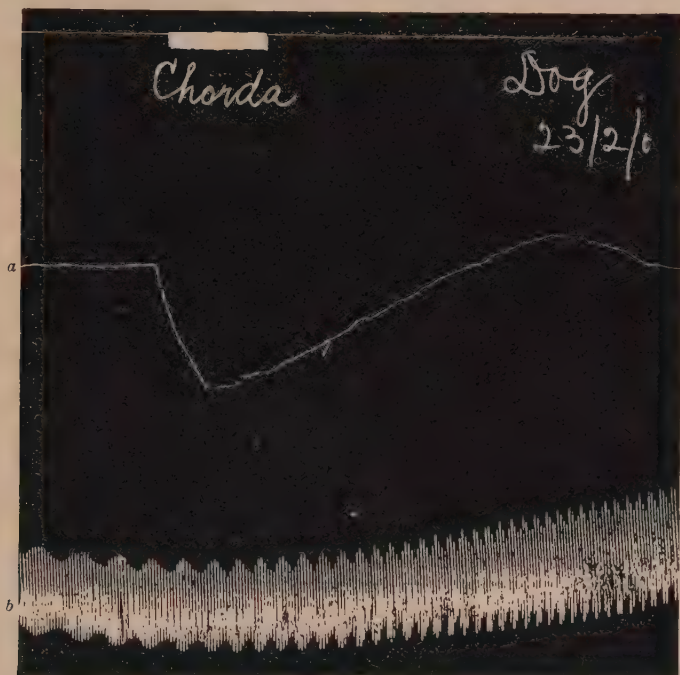


FIG. 152.—Effect of stimulation of the chorda tympani on the volume of the submaxillary gland. (Bunch.)

a, volume of gland; *b*, blood-pressure.

in opposition to this osmotic pressure implies the carrying out of much work by them during secretion. The cells derive the energy required for this purpose from the oxidation of the nutritive materials within them, and therefore use up during their activity more oxygen than during rest. It is found that the amount of oxygen taken up by the submaxillary gland from the blood is enormously increased when the gland is actively secreting (p. 205).

CHANGES IN THE FLOW OF LYMPH.—Although secretion is a vital act, the water and salts of the saliva must be ultimately derived from the blood, since a salivary gland may secrete its own weight of saliva in a few minutes. As the gland-cells take up water and salts from the lymph which bathes them, and as

the percentage of salts in the saliva is less than that in the normal lymph, the latter tends to become more concentrated. This concentration is still further increased by the escape into the lymph of substances of small molecular weight, formed as waste products of the cell activity. As a consequence of its increased concentration, the osmotic pressure of the lymph becomes higher than that of the blood, and water passes by osmosis from the blood into the lymph; in this way an abundant supply of lymph becomes available for the gland-cells, and there is also some increase in the amount of lymph leaving the active gland along the lymphatics.

SECTION IV

DEGLUTITION.—Food is transferred from the mouth to the stomach by the act of deglutition or swallowing. In this process the bolus formed in the mouth is first projected past the anterior pillars of the fauces into the pharynx, then through the pharynx into the œsophagus, and finally along the latter tube into the stomach. It is therefore customary to speak of three stages of deglutition, but it must be remembered that there is no pause between the stages, and that the act of swallowing, once begun, is a continuous one. The first stage of the process, the passage of the food from the mouth into the pharynx, is a voluntary act, the second and third are involuntary.

In the first stage, the jaws are closed and the tongue is raised so as to press against the palate, the latter movement being due to contraction of the mylohyoid muscle, aided by the intrinsic muscles of the tongue itself. At the same time the base of the tongue is drawn slightly backwards by the contraction of the styloglossi and palatoglossi. The second stage then commences.

While the bolus is in the pharynx, the soft palate is raised so as to prevent the passage of food into the nares. The opening into the respiratory tract is guarded in the following manner. The arytenoid cartilages are rotated inwards by contraction of the lateral crico-arytenoid muscles, and approximated by contraction of the arytenoideus. They are at the same time drawn forward by contraction of the thyro-arytenoids, so that the glottis takes the form of a T-shaped slit. Further, the opening of the larynx is diminished in size by contraction of the ary-epiglottidean muscle-fibres; and, by the elevation of the larynx and the drawing back of the tongue, the opening is further guarded by the lower part of the epiglottis (Fig. 153). In addition the true and false vocal cords approximate, thus closing the opening into the lower part of the larynx.

By these means the risk of food passing into the back of the nasal cavity or into the larynx is rendered slight, and it is still further diminished in two ways : (1) The passage of food through

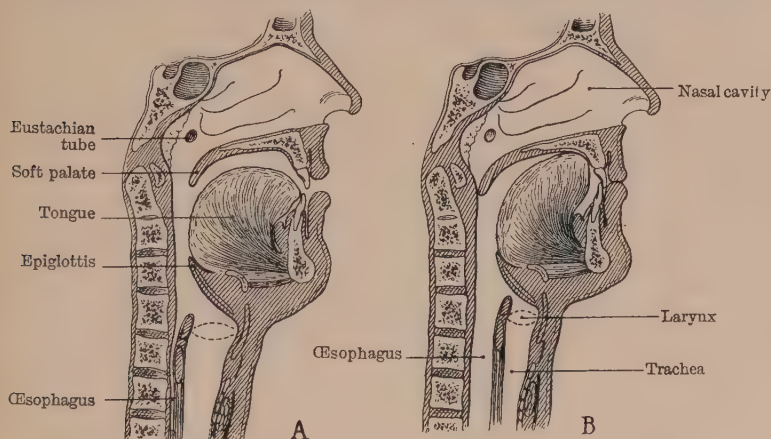


FIG. 153.—A diagram to show the position of the tongue, soft palate, and larynx.

the pharynx is carried out extremely rapidly ; and (2) during swallowing the respiratory movements are inhibited for a few seconds. Even then, it occasionally happens that particles of food “go the wrong way,” that is to say, they enter the larynx and have to be expelled by coughing.

X-RAY OBSERVATION.—The passage of the swallowed material can be observed by the use of X-rays if the food has been mixed with an insoluble salt of barium or bismuth. The bolus of solid food is carried along the oesophagus by a wave of contraction, immediately preceded by a wave of relaxation. In man the wave travels more rapidly in the upper two-thirds of the oesophagus, which contain striated muscle, than in the lower third, the muscle of which is unstriated. When liquid food is swallowed the oesophagus remains in a relaxed condition and the fluid rapidly reaches its lower end, where it is arrested by a constriction at the cardiac opening of the stomach ; it is then slowly forced into the stomach by a wave of contraction. Owing to this difference in the mode of swallowing of liquids and solids, liquid food usually reaches the stomach in from four to six seconds after leaving the mouth, whereas solids take from ten to eighteen seconds. If liquid is swallowed several times in rapid succession, it accumulates in the oesophagus, which remains relaxed until the last of the series of acts of deglutition ; a wave

of contraction then passes down the œsophagus and drives the fluid into the stomach.

THE NERVOUS MECHANISM.—The second and third stages of swallowing are purely reflex and are initiated by the contact of food with certain sensitive spots near the base of the tongue and in the pharynx. This is shown by the observation that swallowing may take place in an unconscious person, and that it can be evoked in an animal whose cerebral hemispheres have been removed. It is usually started voluntarily by forcing food from the back of the tongue on to the sensitive area, but the movements of the larynx, pharynx, and œsophagus cannot be brought about voluntarily, they only occur as a reflex act in response to mechanical stimulation of the sensitive spots in that area. If, for example, one swallows repeatedly until the mouth is free from saliva, further swallowing becomes impossible for a short time. Sherrington has shown that, in the decerebrate animal, some kinds of liquid are more effective than others in producing swallowing. Thus, while a few drops of water placed on the back of the pharynx evoke a single act of deglutition, a few drops of dilute alcohol call forth repeated acts of deglutition, and castor oil is not swallowed at all. It seems clear that the stimulus to deglutition cannot be merely mechanical, but that obscure physical or chemical factors must also be involved. The afferent impulse passes along the glossopharyngeal nerve to a centre in the medulla oblongata, and gives rise to the complicated series of movements just described, each stage of the process apparently initiating the succeeding stage.

The efferent nerves chiefly concerned are: (1) for the voluntary stage, the fifth cerebral nerve to the mylohyoid muscle, and the twelfth nerve to the tongue; (2) for the involuntary stages, the glossopharyngeal and vagus nerves to the muscles of the pharynx, and the vagus nerves to the entire length of the œsophagus.

THE DEGLUTITION CENTRE.—The centre in the medulla oblongata controls each step of the process of swallowing in the pharynx and œsophagus, and even the wave of contraction in the œsophagus is due to impulses passing from the central nervous system to its successive segments; for, when the œsophagus is cut across, it is observed that during deglutition an orderly wave of contraction travels along its whole length, just as in the intact gullet. It has been shown, however, that waves of contraction take place in the lower part of the œsophagus, where the muscular coat consists of unstriped muscle, even when all connection with the central nervous system has been severed. Presumably they are brought about by a local reflex mechanism.

The inhibition of respiration which accompanies swallowing is brought about by impulses passing along the glossopharyngeal nerve to the respiratory centre ; if this nerve is divided, electrical stimulation of its central portion arrests respiration for a period corresponding with that of a normal act of deglutition, namely, five or six seconds.

VOMITING.—This is normally initiated by afferent impulses from the duodenum and stomach. The individual “feels sick.” He salivates freely. Soon, filling the lungs and holding the body in an appropriate position, he firmly contracts his abdominal wall. The cardiac sphincter of the stomach then relaxes, allowing the gastric contents to pass freely into the relaxed œsophagus. The stomach wall contracts, thus aiding the evacuation of that organ. When this is complete the pyloric sphincter relaxes, permitting the emptying of the duodenum.

SECTION V

THE STOMACH AND ITS FUNCTIONS.—The stomach forms a dilated portion of the digestive tube capable of storing considerable quantities of nutritive material, and it thus obviates the necessity of taking food at inconveniently frequent intervals. The food remains in the stomach for three hours, and during this period it is acted upon by the gastric juice, so that, when it afterwards comes under the influence of the more potent digestive juices found in the small intestine, the hydrolysis of the protein constituents is already well advanced, and, as has already been described, the saliva has effected a conversion of much of the starch into dextrin and maltose.

THE COMPOSITION OF GASTRIC JUICE.—Gastric juice may be obtained for analysis by producing a permanent gastric fistula in an animal. Pavlov’s method is to make an incision in the stomach, separating it into a larger and a smaller portion. The larger portion is stitched up and remains in continuity with the digestive tract. The smaller portion is kept separate from the larger by a layer of mucous membrane, and is made to open on the surface of the body (Fig. 154).¹ It is found by experiment that the juice secreted by the small stomach has the same composition as that produced by the large stomach, and also that it is secreted in the same proportional amount when the available extent of mucous membrane is taken into consideration ;

¹ We are indebted to the kindness of Messrs. C. Griffin & Co., Ltd., for permission to use these diagrams.

moreover, it has the advantage of being free from admixture with food.

The juice thus obtained is a clear fluid having a specific gravity of 1003 to 1005, and an acid reaction. It consists of

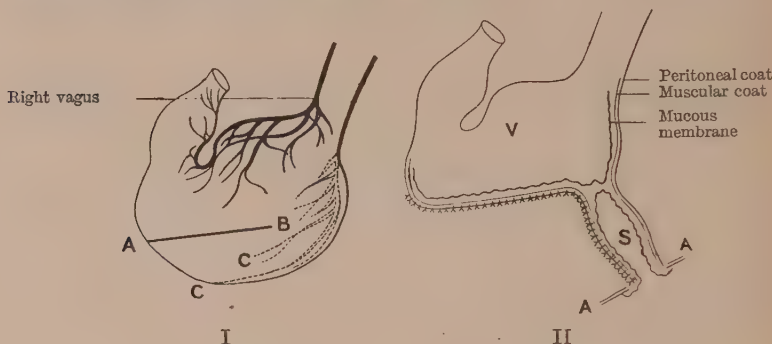


FIG. 154.—Pavlov's method of forming a subsidiary stomach.
(From Pavlov's *Work of the Digestive Glands*.)

I, first stage: A—B, incision. II, lesser stomach completed: S, lesser stomach; A, abdominal wall.

about 99 per cent. of water and 1 per cent. of solids, the latter including mucin, proteins, enzymes, and inorganic salts. The juice also contains free hydrochloric acid in the proportion of about 0.2 to 0.5 per cent. in man; the percentage is rather higher in the dog and other carnivorous animals. The salts are chiefly chlorides and phosphates of potassium, sodium, calcium, and magnesium, the most abundant base being potassium.

THE AMOUNT OF FREE HCl.—This is determined by giving the individual a “test meal” of gruel or weak tea and toast. Fifteen minutes later the gastric contents are removed for analysis by means of a stomach tube. The P_H of the meal is ascertained and the total amount of free acid. The amount is increased in gastric ulcer; it is diminished in cancer and pernicious anæmia. Towards the end of gastric digestion the NaCl increases in the stomach content. It was formerly considered that this was due to the neutralisation of HCl by the base of the saliva or by regurgitated base from the duodenum. Recent work by MacLean and Griffiths has shown that the gastric acidity rises until a maximum P_H is reached between 4.1 and 3.9. At this H ion concentration it remains for a time. Then it falls. The fall is caused by the secretion of a neutral gastric juice rich in pepsin and NaCl.

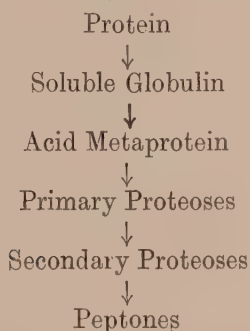
THE FUNCTIONS OF THE GASTRIC JUICE.—It has already been pointed out that the acid of the gastric juice destroys the

pytalin of the saliva, but the hydrolysis of the carbohydrates of the food may be continued, to some extent at least, by the hydrochloric acid in the stomach.

The digestive action of gastric juice can be studied, like that of saliva, by means of experiments in test-tubes. The mucous membrane of a pig's stomach is cut in small pieces and extracted with glycerol. By adding some of the glycerol extract to 0.2 per cent. of hydrochloric acid an artificial gastric juice is obtained.

If a few flakes of fibrin be placed in a test-tube containing such an artificial juice, and the tube be kept at a temperature of 37° C., it will be observed that the fibrin gradually swells up and then dissolves. If the solution is neutralised, a precipitate of metaprotein is formed. If this is removed by filtration, the solution gives a pink colour on the addition of dilute copper sulphate and caustic soda (biuret reaction), owing to the presence of proteoses and peptones. Further analysis of this filtrate shows that several varieties of proteose and at least two kinds of peptone are present. The changes produced in the fibrin are due to the activity of an enzyme, *pepsin*, which, in the presence of dilute hydrochloric acid, brings about hydrolysis of the protein molecule and breaks it up into smaller and more soluble molecules. In normal gastric digestion, the conversion of protein into peptone is not complete when the contents of the stomach are passed on into the small intestine.

THE STAGES OF PEPTIC DIGESTION.—This may be represented in tabular form thus :—



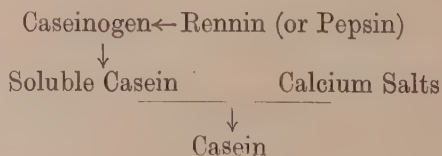
Some proteins which occur in food do not undergo these changes. Thus *elastin* is unaffected by peptic digestion in the time available in the stomach. The *collagen* of connective tissue is probably converted first into gelatin and then into gelatoses and gelatin peptones. The protein constituent of the conjugated proteins is usually converted into proteose and peptone, the prosthetic group being set free. Thus, in the digestion of *nucleo-*

protein by gastric juice, an insoluble residue of nuclein is formed ; in the digestion of *mucin* (gluco-protein), glucosamine is found among the products.

THE CLOTTING OF MILK.—In the stomach there is a conversion of the caseinogen into the nearly insoluble casein. This action of gastric juice has been for many years ascribed to a separate ferment called *rennin*, but latterly evidence has been brought forward which suggests that the formation of casein from caseinogen is due to pepsin itself. The matter has not been conclusively settled, and it will be convenient to retain the term *rennin* in the meantime when describing the effect of gastric juice on caseinogen.

The action of *rennin* can be demonstrated by adding a little neutralised gastric juice to a quantity of milk, and allowing the mixture to stand for a time at a temperature of 37° C. In a few minutes the milk becomes clotted, and after a time the clot shrinks, squeezing out a clear fluid, whey, which contains all the constituents of milk except caseinogen and fat. It can be shown that the fat is entangled in the clot in an unaltered form, so that the coagulation is brought about by the action of the *rennin* on the caseinogen.

THE IMPORTANCE OF CALCIUM.—If a little potassium oxalate is added to milk, the addition of *rennin* does not cause the formation of a clot, though if calcium chloride is subsequently added clotting occurs. Three factors are therefore necessary for the formation of the clot, namely, caseinogen, *rennin*, and lime salts. If *rennin* is added to a solution of pure caseinogen, and the mixture is kept for a short time at a temperature of 37° C., and then boiled to kill the enzyme, the addition of calcium chloride will bring about the formation of casein. Obviously the enzyme has produced some change in the caseinogen, and the only factor required to complete the conversion into casein is the addition of lime salts. There is, therefore, first, a conversion of caseinogen into “soluble casein” by the action of the enzyme, and, second, soluble casein combines with lime salts with the production of insoluble casein. The process may be represented thus :—



It has been stated that gastric juice also acts upon neutral fats, and splits them into glycerol and fatty acids by the agency of an enzyme, *lipase*. The lipase which is found in the stomach may be a constituent of pancreatic juice which has entered the stomach by regurgitation from the duodenum. Pepsin indirectly assists the digestion of fat by dissolving the cell-envelopes of the fat-cells of adipose tissue contained in food. In this way fat is set free and prepared for the subsequent digestive action of pancreatic lipase.

SECTION VI

THE SECRETION OF GASTRIC JUICE.—The mechanism of the secretion of gastric juice may be studied in an animal provided with a gastric fistula in the manner already described (p. 358). When the animal takes a meal, the flow of gastric juice starts five minutes after the beginning of the meal, and continues throughout the period of digestion of the contents of the stomach.

NERVOUS MECHANISM.—It might be supposed that the secretion is brought about by the entrance of food into the stomach, but the following experiment of Pavlov shows that this is not so. The cesophagus of a dog is cut across, and the open, cut ends are sewn to the skin of the neck; a gastric fistula is also made. Food taken by the animal escapes by the upper aperture in the neck, and does not reach the stomach; this is spoken of as “sham feeding,” and it is accompanied by a copious flow of gastric juice showing that the presence of food in the stomach is not necessary in order to excite secretion. Nor is the presence of food in the mouth essential to the production of gastric juice, since, in a hungry animal, the sight or smell of food, or a sound indicating the approach of food, evokes a flow which is quite as abundant as that brought about by a “sham” meal. In these circumstances the stimulus must be a psychical one, the predominant factor in the dog being what, in the absence of a more precise term, is known as appetite; and the secretion thus induced is known as “psychic” or “appetite” secretion.

It is probable, therefore, that the presence of food in the mouth only excites a flow of gastric juice in so far as it arouses appetite, and that the value of palatable and attractive foods as an aid to digestion can be thus explained. Indeed, the effective carrying out not only of gastric but also of intestinal digestion is in large measure dependent on the presence of appetite.

The efferent path for the secretory impulses to the gastric

glands is the vagus nerve, and after section of both vagi neither the presence of food in the mouth, nor the sight or smell of food, causes a flow of gastric juice. Further, it is possible to evoke a flow of gastric juice by stimulating the peripheral portion of the divided vagus nerve. One vagus is divided in the neck, and two or three days later the peripheral end of the nerve is gently drawn to the surface and stimulated with a tetanising current. The heart is unaffected, because the cardiac inhibitory fibres have degenerated, but a flow of gastric juice occurs after a latent period of five minutes. The cause of the long latent period is unknown, though possibly it represents the time occupied by preparatory changes in the gland-cells.

The primary secretion of gastric juice, when a meal is taken, must therefore be regarded as purely reflex in origin, the afferent impulses being caused by the sight, smell, or taste of food, provided that this gives rise to appetite, and the efferent path being the vagus. The secretion is influenced by emotional conditions, pain or depressing emotions tending to inhibit the flow of juice, whereas agreeable emotions favour secretion and thereby assist digestion.

CHEMICAL MECHANISM.—The nervous mechanism just described is not the only factor concerned in the secretion of gastric juice. Certain substances such as histamine, when injected into the blood, provoke a copious flow of gastric juice in a denervated stomach. It was observed by Pavlov that the introduction of food into a dog's stomach was followed, after an interval of from fifteen to forty minutes, by a flow of gastric juice, even after the nervous mechanism had been put out of action by division of the vagus nerves. It was further noticed, under these conditions, that secretion was excited only by certain kinds of foods, such as meat, or meat extract, dextrin or partially digested bread; starch or white of egg produced no secretion. The fact that secretion is brought about by some, and not by all, kinds of foods makes it clear that it does not depend upon mere mechanical stimulation of the gastric mucous membrane, and its occurrence after section of all the nerves supplying the stomach shows that it cannot be nervous in origin.

GASTRIN.—Some light has been thrown upon the means by which the secretion is produced by the experiments of Edkins. This observer has found that, if the pyloric mucous membrane is boiled with water or dilute hydrochloric acid, a decoction is obtained which, when neutralised, filtered, and injected into the blood-stream of another animal, excites a secretion of gastric juice; similar extracts of the mucous membrane of the body of

the stomach do not excite gastric secretion. The conclusion drawn from these experiments is that the presence of partially digested food, or of dextrin or extract of meat, in the stomach, leads to the formation of a hormone by the pyloric mucous membrane. The hormone, which has been called *gastrin*, is believed to be absorbed into the blood-stream, and to be carried by the circulation to the gastric glands, which are thereby stimulated to produce their secretion.

HORMONES.—This term is applied to substances which have the following characteristics. In the first place, they have a relatively small molecular weight, and are easily diffusible. Secondly, each hormone exercises a specific function in exciting or inhibiting the activity of a particular organ or tissue, and, when its function has been performed, it is rapidly destroyed in the body. Thirdly, a hormone does not act as an antigen, that is, it does not excite the production of an antibody which would interfere with the performance of its function. Fourthly, the hormones of the digestive tract are not destroyed by boiling.

THE GASTRIC JUICE PRODUCED BY A NORMAL MEAL.—

The following table from Pavlov illustrates the relative quantity and digestive power of the juice secreted (1) after a normal meal, (2) as a result of the chemical stimulus alone, and (3) after a sham meal, *i.e.* by the nervous secretion alone. The figures indicate the amount of juice secreted by the subsidiary stomach. The digestive power is measured by filling short lengths of narrow glass tube with egg-white, coagulating the latter by heat, and placing the tubes, the ends of which are open, for a given time in the juice to be tested. The digestive power is estimated by the length of the column of coagulated protein which has undergone solution.

Hours.	Normal Meal. 200 gm. Meat into Stomach.		150 gm. Meat into Stomach.		Sham Meal.		Sum of two last Expts.
	Quantity c.c.	Strength mm. dig.	Quantity c.c.	Strength mm. dig.	Quantity c.c.	Strength mm. dig.	Quantity c.c.
1	12.4	5.43	5.0	2.5	7.7	6.4	12.7
2	13.5	3.63	7.8	2.75	4.5	5.3	12.3
3	7.5	3.5	6.4	3.75	0.6	5.75	7.0
4	4.2	3.12	5.0	3.75	0.0	0.0	5.0

It will be observed that the amount of juice secreted as the result of a normal meal, shown in the first column, corresponds

with the totals given in the last column for the nervous and chemical secretions obtained separately.

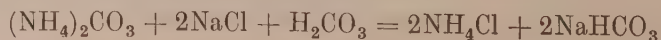
THE ORIGIN OF THE CHIEF CONSTITUENTS OF THE GASTRIC JUICE.—The mucous membrane of the stomach is lined by glands which are of two types, one type being found in the fundus and body, and the other in the pyloric portion, of the organ. The glands of the fundus and body are comparatively straight tubes opening by short ducts on to the inner surface of the stomach. Each gland is lined by cubical, granular cells, which are called *chief* or *peptic* cells; between these cells and the basement-membrane there occur at intervals large, ovoid cells, staining readily with eosin. These are known as *oxyntic* cells, because they are believed to secrete the acid of gastric juice.

The glands in the pyloric region are more twisted, and have longer ducts than the glands of the body of the stomach; they are lined by cells resembling the chief cells, but contain no oxyntic cells.

The cells lining the general surface of the stomach and the ducts secrete the mucin of the gastric juice. The enzymes of the juice are contained in the secretion of the body of the stomach and also in that of the pyloric portion, and are derived from the chief cells of the glands of the body and from the cells lining the pyloric glands. Pepsin, however, does not exist in the secretory cells as such, because extracts of the mucous membrane do not possess marked peptic activity until they have been treated with acid. It is therefore a precursor of pepsin, known as *pepsinogen*, which is found in the secretory cells, and this is converted into pepsin, after its discharge from the cells, by the hydrochloric acid of the gastric juice.

The facts from which it is concluded that the acid itself is derived from the ovoid cells are: (1) that it is most abundant in the middle of the stomach, where these cells are most numerous, and (2) that it is absent from the secretion of the pyloric portion of the stomach, where ovoid cells are wanting.

THE SOURCE OF THE HCl.—Various explanations have been offered as to the method of production of the free acid in the gastric juice. The most probable of these is that the full HCl is produced by a two-stage process. (1) The oxyntic cells secrete into the stomach a solution of ammonium chloride, this being produced from ammonium carbonate, CO_2 and NaCl . Thus:—



(2) The HCl of the ammonium chloride is left behind in the stomach, the ammonia being reabsorbed with the reformation of ammonium carbonate which may be used again.

Four pieces of evidence can be advanced in favour of this view :—

- (1) The oxyntic cells are never acid.
- (2) The gastric mucous membrane is very rich in ammonium salts.
- (3) The cells are permeable to ammonia but not to HCl.
- (4) Less CO_2 is excreted by the lungs during the secretion of gastric juice.

SECTION VII

THE MOVEMENTS OF THE STOMACH.—The movements of the stomach are most conveniently studied by direct observation

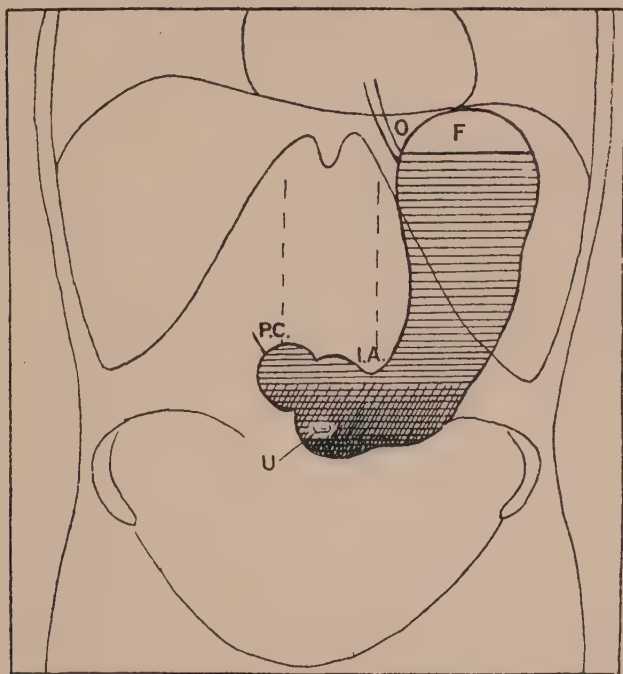


FIG. 155.—Shape of human stomach, in vertical position, shortly after a bismuth meal. (Hertz.)

U, position of umbilicus ; O, œsophagus ; F, fungus ; P.C., pyloric canal ; I.A., incisura angularis.

with the aid of X-rays after the administration of a meal mixed with a quantity of barium sulphate or a bismuth salt. In these

circumstances the organ is seen to consist of a nearly vertical portion, forming an angle with the smaller pyloric portion, which is again subdivided by a constriction into two parts, the *pyloric vestibule*, or *antrum*, and the *pyloric canal* (Fig. 155). The junction of the pyloric canal with the duodenum is marked by the presence of a thickening of the circular layer of the muscular coat, the *pyloric sphincter*. The pyloric canal is about 3 cm. in length, while the pyloric vestibule is less constant in size.

After the ingestion of a meal the muscular walls of the fundus and body of the stomach contract in a tonic manner, and exert a steady pressure upon the contents of the organ. At the same time, rhythmic waves of contraction begin about the middle of the stomach, and travel towards the pyloric sphincter; the waves occur three or four times a minute, and travel so slowly that two or more of them are often visible at the same moment as rings of constriction. The contents of the pyloric vestibule are propelled by these waves towards the pyloric sphincter, and, if this remains closed, they return in an axial stream towards the body of the stomach. The food in the pyloric end of the stomach is in this way thoroughly mixed with gastric juice. As digestion proceeds, the pyloric sphincter opens from time to time to allow the passage of liquid or semi-liquid digested material, known as *chyme*, into the duodenum. Fresh food and gastric juice are forced into the pyloric mill by the steady tonic contraction of the fundus and body. As the contents of the stomach gradually diminish in amount, the organ becomes more tubular in shape (Fig. 156), and it is usually completely emptied in about three hours after a meal.

As the stomach contents diminish in amount, the tonic contraction of the fundus gives place to a rhythmically augmented tonus; by the time the stomach is almost or quite emptied, these assume the form of powerful rhythmic contractions, called *hunger contractions*. In extreme hunger these may be almost continual; with each hunger contraction there is a flow of saliva.

The movements of the stomach are therefore of three kinds: (1) tonic contraction of the fundus and body, and (2) rhythmic waves of contraction in the pyloric portion. The fundus and body thus serve chiefly as a reservoir, in which comparatively little mixing of the food or gastric digestion takes place, although, as already pointed out (p. 349), salivary digestion may continue for some time. At the pyloric end of the stomach the food is thoroughly mixed with gastric juice, and is digested to a considerable extent before being passed on into the duodenum. (3) Hunger contractions of the empty fundus.

In the normal animal the emptying of the stomach is controlled by the pyloric sphincter, and the relaxation of the sphincter

depends on the existence of a peristaltic wave in the pyloric vestibule or antrum. It is stated that each time the wave drives



FIG. 156.—Showing the changes in shape of a cat's stomach after a meal containing a bismuth salt. The numbers indicate the period in hours after the meal was taken. (Edward Arnold.) (From Cannon's *Mechanical Factors of Digestion*.)

the food towards the pylorus relaxation occurs, permitting some of the food to pass. This relaxation is probably inhibited by the presence of undigested food masses in the antrum.

THE NERVOUS SUPPLY.—Lying between the circular and longitudinal layers of the muscular coat of the stomach is a plexus of nerve-fibres with which are associated many nerve-cells (Auerbach's plexus); fibres pass from the plexus to end in relation with the muscle-fibres of the stomach wall. Branches of the vagi and of the splanchnic nerves are distributed to the stomach, the vagus fibres probably ending in synapses in association with the cells of Auerbach's plexus, whereas the sympathetic fibres run directly to the muscle.

Division of the vagus nerves is followed by temporary cessation of gastric movements, and for some time afterwards the movements are defective, with the result that food accumulates and stagnates in the stomach. Stimulation of the peripheral portion of the divided vagus causes brief inhibition followed by increased muscular tone and more vigorous rhythmic contractions (Fig. 157).

Conversely, stimulation of the splanchnic nerve lessens the tone of the fundus and body of the stomach, and abolishes the rhythmic movements of the pyloric part (Fig. 158).

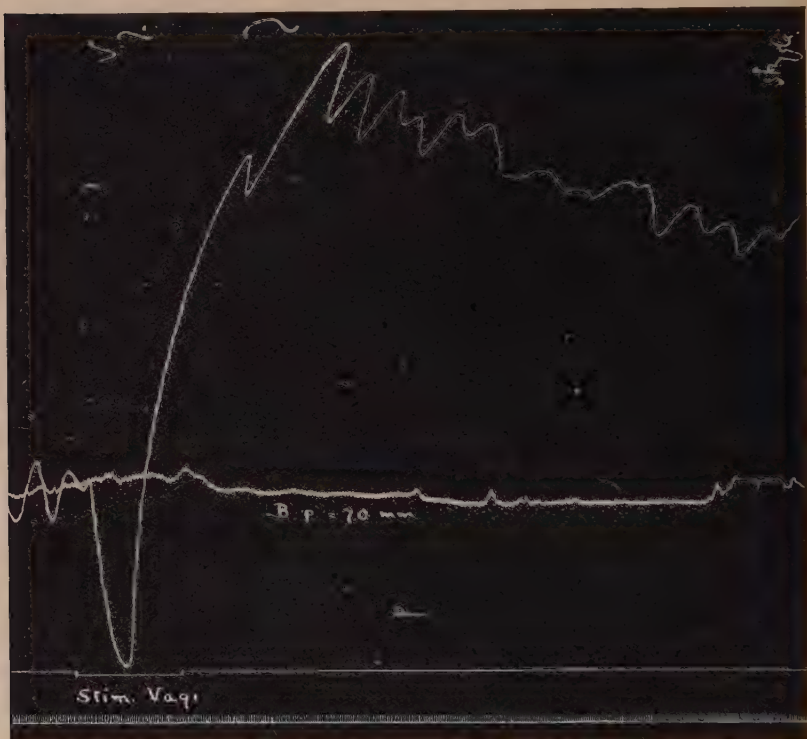


FIG. 157.—Tracing showing initial relaxation followed by contraction of the muscular wall of the stomach on stimulation of vagus nerves. (Elliott.)

It has also been observed by means of X-rays that, in the normal animal, emotional disturbances, such as anger or fear, may produce immediate cessation of the movements of the stomach, and that it remains quiescent until the emotion has passed off. After section of the splanchnic and vagus nerves, emotion does not modify the movements of the organ. It is clear not only that the movements of the stomach can be affected by impulses from the central nervous system, but also that psychical disturbances, particularly those of a depressing character, may affect these movements and thereby interfere with the normal progress of gastric digestion.

The movements of the stomach, although they are influenced

by the central nervous system, are not dependent upon it, since they may continue in a normal manner when the organ is excised

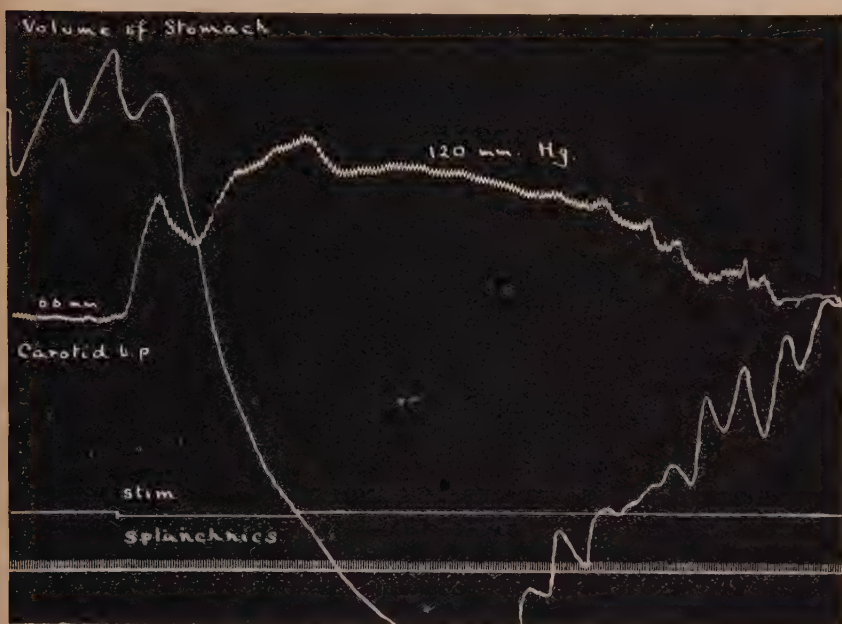


FIG. 158.—Tracing showing relaxation of the muscular wall of the stomach of a cat on stimulation of splanchnic nerves. (Elliott.)

and placed in warm oxygenated Ringer's solution. They are probably brought about by a local reflex through Auerbach's plexus, and are aroused by the distension of the stomach by food.

CHAPTER XV

INTESTINAL DIGESTION

SECTION I

DIGESTION IN THE SMALL INTESTINE.—If an experimental meal is given to an animal in which a fistula has been made just beyond the pylorus, it is found that food begins to pass from the stomach into the intestine eight to twelve minutes after the meal is taken. The rate of escape of the food from the stomach is indicated in the following table:—

1st hour	.	.	.	.	.	32·6	per cent.
2nd „	.	.	.	.	.	17·9	„
3rd „	.	.	.	.	.	29·5	„
4th „	.	.	.	.	.	1·87	„
5th „	.	.	.	.	.	6·66	„
6th „	.	.	.	.	.	4·21	„

If the material collected in this way is analysed, it is found that 67 per cent. of the nitrogen is in the form of proteose and peptone, and that, of the starch of the meal, 21 per cent. has been converted into dextrin and 4 per cent. into sugar. The whole of the protein and carbohydrate of the meal is accounted for, no absorption of these substances, or of fat, having taken place in the stomach. The mixture of semi-digested substances which enters the intestines has a yellowish colour and a semi-fluid consistence, and is immediately subjected to the action of the pancreatic juice and bile. The secretion of Brunner's glands and the intestinal juice are also mixed with the duodenal contents, but the digestive action of the former is not known to have any importance, and that of the latter has its chief value in the later stages of the digestive process. The action of the pancreatic juice and bile must therefore be first considered.

THE COMPOSITION OF PANCREATIC JUICE.—Pure pancreatic juice may be obtained from an animal either by means of a temporary fistula, made by introducing a cannula into the

pancreatic duct, or by a permanent fistula. In the dog there are two ducts, the larger of which opens into the duodenum about an inch below the entry of the bile duct. Pavlov's method of making a permanent fistula is to cut out a patch of the duodenal wall with the opening of the duct in its centre, stitch up the gap in the duodenum, and suture the patch with the opening of the duct into the abdominal wall.

The pancreatic juice obtained in this way is a clear, limpid fluid, having a strong alkaline reaction. The degree of alkalinity is such that equal volumes of gastric juice and pancreatic juice neutralise each other. The concentration of pancreatic juice varies considerably, but it contains on an average about 3 to 4 per cent. of solids. Its composition does not vary with the type of food eaten. The solids consist of nucleo-protein, enzymes or their precursors, and inorganic salts; the chief salts are sodium carbonate and sodium chloride. The action of the pancreatic juice on the constituents of the food may be studied in test-tubes, using either the secretion obtained from a fistula, or an artificial juice made by adding a glycerol extract of the fresh gland to a solution of sodium carbonate of such a strength that the mixture contains 0·5 per cent. of the carbonate.

PANCREATIC JUICE ON PROTEINS.—Pure pancreatic juice, obtained directly from the pancreatic duct without contact with the intestinal mucous membrane, has no action on proteins. If, however, the juice has flowed over the duodenal mucous membrane, or has been mixed with intestinal juice, it is strongly proteoclastic. The active proteoclastic ferment is called *trypsin*, and is derived from an inactive precursor present in pure pancreatic juice and known as *trypsinogen*. Since a mere trace of intestinal juice is capable of activating an unlimited amount of pancreatic juice, the activation of trypsinogen is believed to be effected by a ferment, *enterokinase*, present in intestinal juice and formed by the mucous membrane of the small intestine. Trypsinogen appears to be trypsin which has been rendered inactive by being combined with a protein which it cannot digest. This protein, particularly in the presence of calcium salts, is rapidly digested by enterokinase, thus liberating the trypsin.

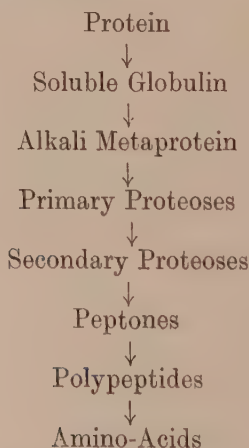
If a few flakes of fibrin are placed in a solution containing trypsin and 0·5 per cent. of sodium carbonate in a test-tube, and kept at a temperature of 37° C., the fibrin will begin to be eroded in a few minutes, and gradually it will be dissolved. The products in solution will vary according to the time during which digestion has been allowed to proceed, but, generally speaking, the course of hydrolysis is the same as in peptic digestion, except

that, as the process takes place in an alkaline medium, the metaprotein formed is alkali and not acid. A second point of difference is that the intermediate stages are passed through more rapidly in pancreatic than in gastric digestion; and, thirdly, amino-acids are produced in tryptic but not in peptic digestion.

In the normal course of digestion in the intestine, the final conversion of peptone into amino-acids is largely effected by the ferment, *erepsin*, which is contained in the intestinal juice.

If tryptic digestion of fibrin or casein has been allowed to proceed for some days, the solution contains the amino-acid derived from these substances (p. 4). One of these, namely, tryptophane, is split off comparatively early in tryptic digestion; its presence may be detected by the appearance of a reddish-purple colour when bromine water and acetic acid are added to the tryptic digest. Leucine and tyrosine are also easily demonstrated in the digest, and crystallise out readily if the fluid is concentrated. Tyrosine appears as sheaves of colourless needles, and leucine, which is the more soluble of the two, occurs in the form of a colourless spheroidal clump, which sometimes shows concentric and radial striation. Solutions of tyrosine, when boiled with Millon's reagent, give a red colour.

THE STAGES OF TRYPTIC DIGESTION.—These may be represented in tabular form thus:—



The earlier stages of tryptic digestion of protein are most efficiently carried out in a slightly alkaline medium, but the ferment is active in either an alkaline or a neutral solution. Under natural conditions, the alkaline pancreatic juice and bile are nearly neutralised by the acid contents from the stomach,

and the contents of the small intestine throughout its length are almost neutral. The activity of trypsin diminishes during the course of normal digestion, since the ferment enters into combination with the products of its own activity, that is, with amino-acids and peptones, and in this way it becomes inactive. The intestinal contents taken from the lower end of the ileum show very little tryptic activity.

THE ACTION OF PANCREATIC JUICE ON STARCH.—The action of pancreatic juice on starch depends on the presence of an enzyme, *amylase*. By means of this ferment starch is converted into maltose, as in the case of salivary digestion (p. 349), but the action of pancreatic amylase is more rapid and powerful than that of the ptyalin of saliva. If some pancreatic extract is added to dilute starch paste kept at a temperature of 37° C., the starch is converted into soluble starch in a few seconds, and erythro-dextrin may be detected in half a minute. Moreover, the pancreatic juice is capable of digesting unboiled starch, on which saliva has no action.

THE ACTION OF PANCREATIC JUICE ON FATS.—If perfectly neutral fat, such as pure olive oil, be shaken up with pancreatic juice, and the mixture be kept at a temperature of 37° C., the fatty ester will be hydrolysed, yielding fatty acid and glycerol, and the reaction of the fluid will become acid. The agent which brings about this change is an enzyme, *lipase*, which is a constituent of the pancreatic juice. Mellanby, however, regards this enzyme as of small value. His experiments showed that bile is a far more potent factor in fat digestion. (See later.)

THE ACTION OF PANCREATIC JUICE ON MILK.—A milk-curdling ferment has been described as occurring in the pancreatic juice, and it is a fact that clotting of milk takes place when the juice is mixed with milk at the temperature of the body. It is doubtful, however, whether a separate ferment is present in the pancreatic secretion, and the milk-curdling function has been ascribed by some authorities to trypsin; moreover, the presence of rennin in the pancreatic juice would seem to be unnecessary in view of the active milk-curdling property of gastric juice.

SECTION II

THE SECRETION OF THE PANCREATIC JUICE.—In an animal with a permanent pancreatic fistula, a flow of juice is seen

to begin within five to twenty minutes after the ingestion of a meal. The secretion is largely increased two or three hours later, when the contents of the stomach are passing into the duodenum in largest amount, and it comes to an end in about five hours.

PANCREATIC SECRETION AFTER MEAL OF 600 C.C. OF MILK.

Hour after Feeding.	Quantity of Juice in c.c.	
1st	8.75	8.25
2nd	7.5	6.0
3rd	22.5	23.3
4th	9.0	6.25
5th	2.0	1.5
Total	49.75	45.3

The formation of pancreatic juice coincides with the passage of the acid gastric contents into the duodenum. Three factors very probably contribute in bringing about the secretion of the pancreas: the hormone secretin, the bile-salts, and the vagus nerve.

SECRETIN.—Bayliss and Starling showed that the flow of juice which occurs under these conditions cannot be due to a nervous reflex, since the introduction of acid into a loop of small intestine is followed by a flow of pancreatic juice, even when all the nervous connections of the loop of gut with the rest of the body have been destroyed. Hence the stimulus must be a chemical one, some substance being liberated from the intestinal epithelium and carried in the portal blood-stream to the general circulation and so eventually to the pancreas. This substance is *secretin*. It may be extracted by grinding duodenal mucous membrane with sand in absolute alcohol (Mellanby). The extract is dissolved in water. Fats are precipitated by calcium chloride. The secretin is dissolved and precipitated until sufficiently pure. Its effects are shown in Fig. 159. It is, however, destroyed by both acids and alkalies at 100° C. It belongs to the group of hormones or “chemical messengers,” the chief characteristics of which have already been described (p. 363).

Convincing proof that the pancreas is excited by the presence of a hormone in the blood is provided by the experiment of crossed circulation: the blood of a dog, A, is led into the vessels of another dog, B; if acid is introduced into the duodenum of A there is a secretion of pancreatic juice in dog B. Secretin is absorbed directly into the blood, reaches both liver and pancreas via the circulatory system and causes both to secrete.

Secretin appears to be present as such in the duodenal mucous membrane. According to Mellanby it is carried into the blood-stream by the bile-salts during their absorption. Further, it is

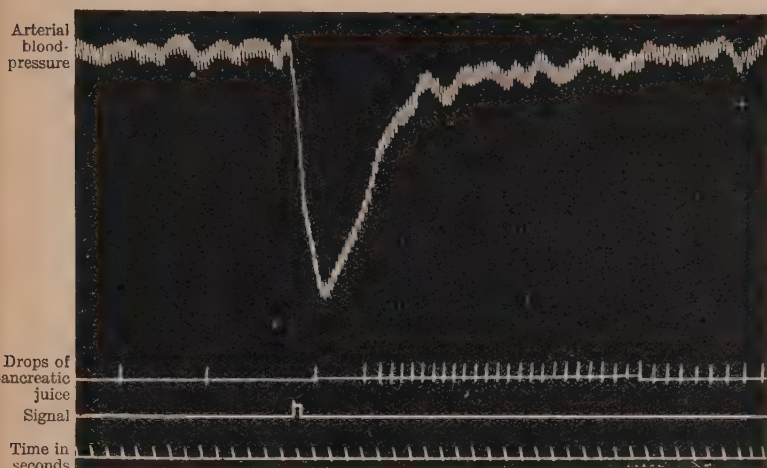


FIG. 159.—Effect on blood-pressure, and on the secretion of pancreatic juice, of the injection of a solution containing secretin. (Bayliss and Starling.) (From Schafer's *The Endocrine Organs*.)

possible that bile-salts themselves may stimulate the pancreas. It should be noted that the flow of juice produced by secretin (+ bile-salts?) is very free but not very rich in enzymes.

THE VAGI ON THE PANCREAS.—A nervous factor is also concerned in the production of pancreatic juice, comparable with the reflex which brings about the first secretion of gastric juice; and Pavlov has shown that stimulation of the vagus will excite a flow of pancreatic juice, even when the pylorus of the stomach is ligatured so as to prevent the passage of the acid contents of the stomach into the duodenum. This juice is much more concentrated and active than the "secretin" juice. The first few c.c. of juice secreted is nervous in origin, because the juice first formed appears a few minutes after a meal is taken, and, further, it differs in character from that formed later, being more viscid, richer in ferments and in protein constituents, and poorer in alkali than the latter.

THE CHANGES IN THE PANCREAS WHICH ACCOMPANY SECRETION.—The pancreas is a compound tubular gland, and it contains, in addition to the ordinary secretory tubules, clumps of

cells which do not stain deeply with the ordinary dyes, and which are known as cell-islets of Langerhans. These islets are concerned with the formation of insulin, and their function will be discussed in connection with metabolism. The secretory tubules of the pancreas are lined by a single layer of columnar cells, each of which shows two zones—an outer, which stains with basic dyes such as

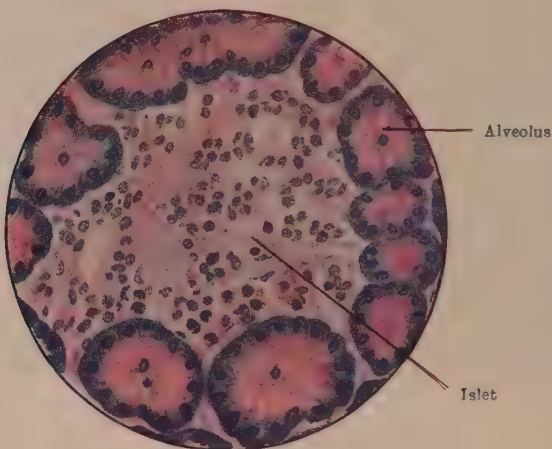


FIG. 160.—A section of the pancreas of a dog. $\times 300$.

hæmatoxylin, and an inner, filled, in the resting stage of the gland, with secretory granules (Fig. 160), which stain well with eosin, or neutral gentian.

After a prolonged period of secretory activity the granules are greatly diminished in number, and the inner zone of the cell is relatively and absolutely smaller as compared with the outer zone. Under normal conditions this diminution of the inner zone does not occur, because the formation of new granules keeps pace with the extrusion of those previously formed, so that the appearance of the cells is little altered by the secretion required for an ordinary meal. The secretory granules are in all probability zymogens, and represent the precursors of the enzymes found in the juice. In the case of trypsinogen, the precursor has received the name of *protrypsinogen*.

SECTION III

THE COMPOSITION OF THE BILE.—Bile may be obtained for analysis from the gall-bladder of a recently killed animal, or it may be collected from a gall-bladder fistula during life. Its

composition, however, is not the same in the two cases, fistula bile being much more dilute than bile which has been stored for a time in the gall-bladder. The difference is shown in the following two analyses of human bile by different observers:—

Fistula Bile.		Gall-Bladder Bile.	
Mucin and pigments .	0·148	Mucin	1·29
Sodium taurocholate	0·055	Sodium taurocholate	0·87
Sodium glycocholate	0·165	Sodium glycocholate.	3·03
Cholesterol	—	Cholesterol	0·35
Lecithin	0·038	Lecithin	0·53
Fats	—	Fats	0·73
Inorganic salts	0·840	Soaps	1·39
Water	98·7	Water	91·81

Bile thus becomes greatly concentrated by the absorption of water during the time it remains in the gall-bladder. It is a viscid fluid, golden brown in carnivora, green in herbivora, and it possesses a bitter taste. The viscosity is due to the presence of mucin in human bile, and of a nucleo-protein in that of the ox and some other animals. The colour depends upon the presence of the bile-pigments, bilirubin and biliverdin. The former is more abundant in the bile of carnivora, the latter in the bile of herbivora. The proportion appears to vary in human bile according to the nature of the diet. The bitter taste of bile is due to the bile-salts, glycocholate and taurocholate of sodium. In dog's bile only the latter is present. Further details of the chemistry of the bile will be found in Chapter XX.

THE FUNCTIONS OF THE BILE.—Bile is not a digestive juice in the proper sense of the term. It is said to contain a weak amyloclastic enzyme, but the action of this ferment is quite insignificant. Nevertheless the bile exercises important functions in connection with the process of digestion. (1) The acid meta-protein and the proteoses resulting from the gastric digestion of proteins are precipitated by the bile-salts in the duodenum. This conversion of a fluid or semi-fluid material into the solid condition will retard its progress along the intestine and allow more time for the action of the pancreatic juice. (2) The bile-salts act as assistants to each of the principal ferments of the pancreatic juice, that is, they increase the rate of the digestive process without themselves taking any active part in it. In the presence of bile-salts the power of the pancreatic enzymes amylase, trypsin, and lipase is increased, the most pronounced effect being that on the lipase. The adjuvant action

of bile in digestion is due to the property which the bile-salts possess of reducing surface tension, and to their power of dissolving fatty acids and soaps. By the reduction of surface tension the fats are emulsified easily. (3) Bile promotes the absorption of the products of digestion, this property also being due to the bile-salts. Free fatty acids are brought into solution, and in this form are more adapted for passing through the epithelial cells of the intestinal villi. The importance of the presence of bile for the digestion and absorption of fat is shown by the fact that, when bile is prevented from entering the intestine, 60 per cent. of the fat of a meal passes into the fæces, as compared with about 5 per cent. under normal conditions. (4) Bile is said to stimulate the peristaltic movements of the intestine, and (5), as already pointed out, the reabsorbed bile-salts stimulate the liver to further secretion. (6) Lastly, it causes the passage of "secretin" into the blood and so stimulates pancreatic secretion.

THE SECRETION OF BILE.—The secretion of bile is a continuous process, and, in periods when digestion is not taking place, bile accumulates in the gall-bladder, where it rapidly undergoes concentration. The rate of production of bile has been studied in animals with experimental fistulæ, and also in man when fistulæ have formed in the course of disease. It is found in man that something less than a litre of bile can be collected from a fistula in twenty-four hours, an amount equal to that of the juice secreted by the pancreas in the same time.

So far as is known, the secretion of bile is independent of nervous action, and is excited by the reabsorbed bile-salts, possibly aided by secretin. The flow from a fistula is fairly continuous, though it varies in rate with the period of the day and with other conditions. The rate of flow in such a case is, of course, unaffected by reabsorption of bile-salts. It is increased by the introduction of dilute hydrochloric acid into the duodenum. The rate of secretion of bile, like that of the pancreatic juice, varies with the nature of the food, and for the same reason is greater when a meat diet is taken, and less when the food consists mainly of carbohydrates. Fatty food, which inhibits the secretion of gastric juice, excites the secretory activity of the pancreas and liver, though not to the same extent as does meat.

THE FINAL STAGES OF THE DIGESTIVE PROCESS.—Saliva, gastric and pancreatic juice in turn carry the digestion of the foodstuffs to a certain point. The pancreatic juice converts proteins into peptones and amino-acids; it converts starch into maltose, but has no action upon cane-sugar or lactose,

and little or no action upon maltose. The completion of the digestive process is the function of the intestinal juice.

SECTION IV

THE COMPOSITION OF THE INTESTINAL JUICE.—Intestinal juice is obtained, like the other digestive secretions, by means of a fistula. A segment of intestine of sufficient length is separated by incisions; one end of the separated portion is closed by sutures, and the open extremity is sutured into the abdominal wall, the continuity of the remainder of the bowel being restored by stitching the free ends together. The detached segment retains its normal blood-supply. In another method, both ends of the segment are left open, and each is sutured separately into the abdominal wall.

The juice obtained from such a fistula has a specific gravity of about 1010, and is alkaline. It contains 1 to 2 per cent. of solids, half of which are organic and half inorganic. The organic solids consist mainly of serum-albumin, serum-globulin, and enzymes. The chief inorganic substances are sodium chloride and sodium bicarbonate.

THE FUNCTIONS OF THE INTESTINAL JUICE.—It has already been pointed out that the intestinal juice converts trypsinogen into trypsin by virtue of the enzyme, *enterokinase*, which it contains, and also that another of its enzymes, *maltase*, completes the digestion of starch by converting maltose into glucose. Each molecule of maltose takes up a molecule of water, and is split into two molecules of glucose:—



The intestinal juice also contains two enzymes which convert the di-saccharides, cane-sugar and lactose, into mono-saccharides. One of these ferments, *invertase*, converts a molecule of cane-sugar into one molecule of glucose and one molecule of fructose. The other, *lactase*, hydrolyses lactose in a similar way with the formation of glucose and galactose. Lactase is most abundant in young animals, at the period of life when lactose is an important constituent of the dietary. The terminal stages of the hydrolysis of protein are effected by a ferment, *erepsin*, existing in the intestinal juice. Erepsin acts upon proteoses and peptones, splitting them up into amino-acids. Erepsin is also contained in the epithelial cells covering the villi, and it is possible that the final stages of hydrolysis may occur to some extent in these cells.

The chief amino-acids resulting from the digestion of proteins are leucine, tyrosine, aspartic acid, glutamic acid, tryptophane, cystine, lysine, arginine, and histidine.

THE SECRETION OF THE INTESTINAL JUICE.—The intestinal juice is produced by the crypts of Lieberkühn, which are tubular glands lined by columnar epithelium, occurring in the mucous membrane of the small intestine, and opening between the bases of the villi. There is no evidence that the secretion is influenced by a nervous factor. The normal stimulus for the secretion of the intestinal juice is undoubtedly secretin, and possibly also other hormones. This possibility is supported by the fact that intestinal juice is produced in the dog about ten minutes after the ingestion of a meal of meat, and that the flow is increased in the third hour after the food has been taken. The secretion of intestinal juice can also be brought about by mechanical stimulation of the intestinal mucous membrane.

THE PROGRESS OF DIGESTION IN THE SMALL INTESTINE.—Experiments have been made in which the intestinal contents of dogs were withdrawn, by means of appropriate fistulæ, at different stages of their passage along the bowel. It has been found that, after a test-meal, 77 per cent. of the protein is converted into proteose and peptone, and one-half to three-fifths of the starch into dextrin and sugar, as a result of gastric and duodenal digestion, and that, when the intestinal contents reach the lower end of the ileum, the digestion of all the food-stuffs is complete.

The final result of the action of the digestive juices on the foodstuffs is, therefore, their conversion into amino-acids, monosaccharides, fatty acids, soap, and glycerol; and consideration of the process whereby this is effected shows that it possesses two striking features. One is the extent to which each stage of the process is correlated with, and dependent on, the preceding stage. The other feature is the gradual replacement of nervous by chemical control of the secretions in successive stages of digestion. The production of saliva is purely reflex in origin, that of gastric juice partly nervous and partly chemical, and that of bile, pancreatic juice, and succus entericus entirely, or almost entirely, due to chemical stimuli.

SECTION V

THE MOVEMENTS OF THE SMALL INTESTINE.—The intestinal contents are slowly propelled along the gut towards

the colon, and at the same time they are subjected to a continuous mixing process. The movements may be observed in a living man or animal by X-rays after the administration of a barium or bismuth meal. They can also be observed directly, if the abdomen of an anæsthetised animal is opened and the intestines are immersed in warm saline solution. The movements may then be recorded by a balloon inserted in the lumen of the bowel connected with a tambour and writing lever; contraction of the intestinal wall compresses the balloon, thus forcing air into the tambour, thereby raising the lever.

The movements observed consist of peristalsis and segmentation.

PERISTALSIS can be produced experimentally by introducing into a loop of intestine a bolus of cotton-wool smeared with vaseline. Immediately above the bolus a narrow ring of constriction is formed by the contraction of both muscular coats, whereas below the bolus the muscular wall is relaxed for a distance of 2 or 3 centimetres. The ring of constriction travels slowly along the intestine as a wave, pushing the bolus before it towards the colon, and always preceded by the zone of relaxation. A similar wave of peristalsis can be set up by pinching the gut. These experiments demonstrate the chief features of peristalsis: (1) that a stimulus applied at any point of the small intestine produces contraction above, and relaxation below, the point of stimulation, and (2) that both the contraction and the relaxation travel as a wave at the rate of 1 to 2 centimetres a minute, and always towards the colon. The normal stimulus to peristalsis is the presence of a bolus of food, and the character of the movement is such that the wave of contraction drives the food into a region of the intestine which is already relaxed, and thereby prepared to receive it.

Occasionally a more rapid peristaltic wave travels along the bowel. This is known as "peristaltic rush," and is seen, for example, when purgation occurs.

Peristalsis continues in a normal fashion when all the nerves passing from the central nervous system to the intestine have been divided, but it is abolished by painting the wall of the intestine with cocaine or nicotine, which puts the myenteric plexus out of action. It is concluded, therefore, that peristalsis is brought about by a local reflex mechanism, situated in Auerbach's plexus (the myenteric plexus), the impulse to the plexus being evoked either by distension of the intestinal wall, or by the action of irritant substances upon the nerve-endings in the mucous membrane.

SEGMENTATION.—The segmenting contractions are most readily observed in a normal animal after the administration of a bismuth meal. The process consists in the sudden appearance of narrow rings of constriction in a previously quiescent loop of intestine. The constrictions divide the loop into a number of segments, and give it the appearance of a string of sausages. These constrictions, represented by *a, a, a, a* (Fig. 161), rapidly

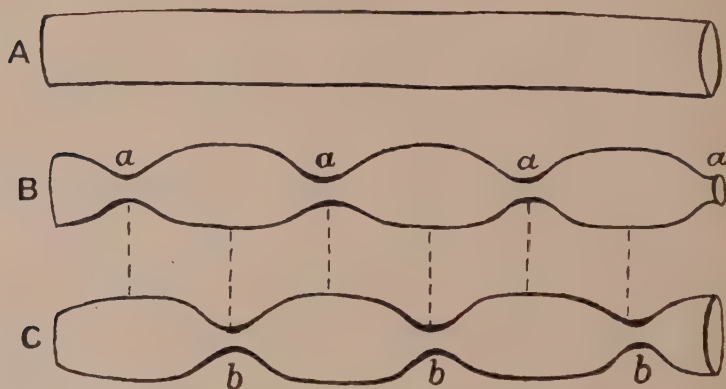


FIG. 161.—Diagram showing segmenting contractions of small intestine.
A. Intestine at rest. B. Segmenting contractions at *a, a, a, a*.
C. Later stage, contractions at *b, b, b*.

disappear, and are succeeded by fresh constrictions, *b, b, b* (Fig. 161), starting at the centres of the segments just formed; as a result the original segments are divided in half, and the halves of adjacent segments reunite to form fresh segments. This process of segmentation is repeated seven or eight times a minute in man, and may continue for half an hour or more in the same loop of intestine. It has a two-fold effect. In the first place, it ensures thorough mixture of the food with the digestive juices and thereby assists digestion, and, in the second place, by continually bringing fresh portions of the intestinal contents into contact with the mucous membrane, it facilitates the absorption of the products of digestion. Both layers of the muscular coat take part in these contractions, as well as in the peristaltic waves, but the segmenting contractions do not cause any onward movement of the intestinal contents towards the colon. The rhythmic character of these movements is well shown by inserting a balloon into a loop of intestine, and connecting it with a piston-recorder in order to obtain a graphic record.

The normal stimulus to rhythmic segmenting contractions is probably distension of the intestinal wall by a bolus of food, and

since they take place in loops of intestine after removal from the body, these contractions cannot be dependent upon impulses proceeding from the central nervous system. Since they are unaffected by nicotine or cocaine, which put the myenteric plexus out of action, the segmental contractions are probably purely myogenic in origin, and due to a direct response of the muscle to increased tension. This view is supported by the observation that rhythmic contraction can take place in isolated strips of intestinal muscle from which the myenteric plexus has been removed.

It must not be imagined that segmentation and peristalsis are taking place simultaneously throughout the whole length of the small intestine, for, as stated above, the inhibitory phase which precedes the peristaltic contractions extends for some distance, and involves quiescence of the whole muscular coat until it has passed along.

THE NERVES OF THE SMALL INTESTINE.—The small intestine is supplied by the vagus and the sympathetic (splanchnic) nerves, and although, as has been pointed out, the

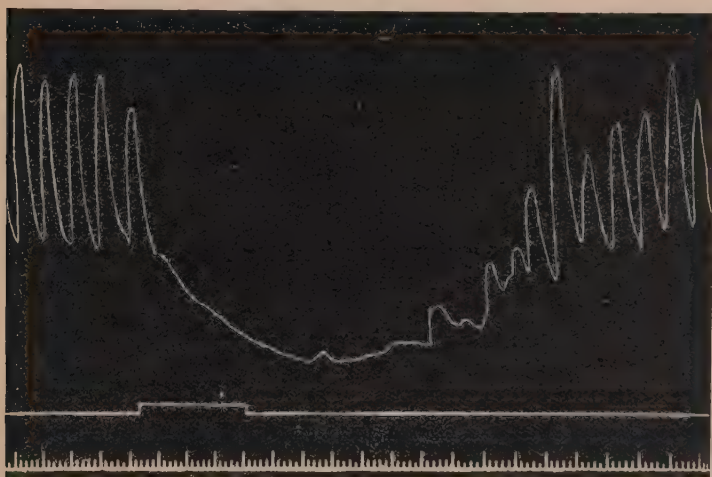


FIG. 162.—Tracing showing cessation of rhythmic segmental contractions and relaxation of the intestinal wall on stimulation of the splanchnic nerve (balloon method). (Bayliss and Starling.)

Fall of lever = relaxation.

intestinal movements are independent of the central nervous system, it can be shown that these nerves exert a controlling influence. Stimulation of the vagus is followed by contraction

of the muscle of the intestinal wall after a preliminary relaxation, but has no effect on the ileo-colic sphincter. Stimulation of the splanchnic nerve results in a cessation of both segmentation and peristalsis (Fig. 162), but in contraction of the ileo-colic sphincter. The vagus and sympathetic fibres to the small intestine are distributed to the myenteric nerve-plexus lying between the layers of the muscular coat. The influence of the central nervous system on the intestinal movements is shown in their inhibition as a result of pain, anger, or anxiety, and also in their exaggeration in consequence of emotional excitement.

THE EFFECTS OF DRUGS.—The movements of the intestinal wall are increased by pilocarpine, which stimulates the nerve-endings of the vagus. The nerve-endings are paralysed by atropine, the effect of which is antagonistic to that of pilocarpine.

A piece of intestine immersed in oxygenated Ringer's fluid at the temperature of the body shows segmenting contractions, which can be recorded by means of a lever connected with the piece of intestine. When adrenaline is added to the Ringer's fluid, the contractions cease.

THE PASSAGE OF THE INTESTINAL CONTENTS FROM THE ILEUM INTO THE CÆCUM.—The ileo-colic sphincter is usually closed, and observations with the aid of X-rays show that the material in the small bowel tends to accumulate behind it. From time to time the sphincter relaxes, and a considerable quantity of the contents of the lower part of the ileum passes into the cæcum and ascending colon. The immediate cause of the relaxation of the sphincter appears to be a nervous reflex (gastro-ileac reflex), which follows the entrance of a fresh meal into the stomach. The delay in the ileum will obviously favour the absorption of the last traces of nutritive substances.

SECTION VI

ABSORPTION IN THE SMALL INTESTINE.—The absorption of the foodstuffs is almost entirely limited to the small intestine. No water is absorbed in the stomach, and only minimal amounts of peptone, sugar, and alcohol. Considerable amounts of fluid are absorbed in the large intestine, and possibly a small amount of glucose also, but, in normal circumstances, the material which reaches the large bowel is free from sugar, and almost free from other nutritive digestive products.

The process of absorption can be investigated by collecting

the intestinal contents by means of fistulæ after the ingestion of a weighed meal, and analysing them. For example, after a meal of bread given to a dog, it was found that there was no absorption in the stomach. About 17 per cent. by volume was absorbed in the duodenum; by the time the jejunum was reached, nearly 38 per cent. had been absorbed, and this amount rose to 68 per cent. in the ileum and 94 per cent. in the cæcum. But practically all the nutrient material had been absorbed in the ileum.

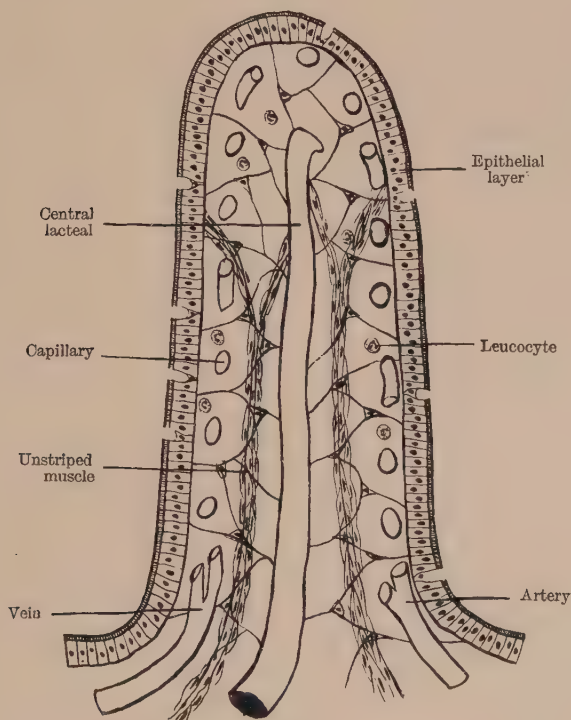


FIG. 163.—Diagram of a villus.

Absorption takes place through the villi of the small intestine, partly direct into the blood-stream, and partly by way of the lymphatic system, the food material in the latter case reaching the blood-vessels along the thoracic duct.

A *villus* (Fig. 163) is a finger-like projection of the mucous membrane, covered by columnar epithelium, each cell having a refractive, striated border at its free end, and resting by its deep extremity on a basement-membrane. In the centre of the villus is a lymphatic vessel, the central lacteal, beginning in a

blind extremity and communicating with the plexus of lymphatic vessels in the submucosa. Between the lacteal and the basement-membrane is retiform tissue with scattered leucocytes and strands of smooth muscle, the latter extending from the muscularis mucosæ and being attached to both basement-membrane and lacteal. A tiny artery is supplied to each villus and breaks up into a plexus of capillaries, lying immediately under the basement-membrane and reuniting to form a small vein.

THE PROCESS OF ABSORPTION.—The function of the villi is greatly to increase the absorbing surface of the intestinal epithelium. Though their size and numbers vary in different parts of the small intestine, there may be upwards of 20 villi to each square millimetre of bowel surface, the absorbing surface of which may be thereby multiplied by from 7 to 18 times. Capillary blood-vessels lie directly beneath about one-third of this area, so that the actual capillary surface available for diffusion exchanges is of the order of 4 square mm. per square mm. of bowel.

The absorption of the products of digestion is effected by what, in the absence of a more precise definition, is called the vital activity of the epithelial cells of the intestinal mucous membrane. Experiments show that the process cannot be accounted for by filtration, diffusion, and osmosis. If, however, the epithelial cells are injured, for instance, by means of sodium fluoride, absorption is entirely regulated by the processes of diffusion and osmosis, and is therefore incomplete. Evidence will be given later that structural changes accompany the absorption of both protein and fat. Experiments with dyes soluble in lipoids show that these enter the cells themselves. On the contrary, dyes insoluble in lipoids have been shown to pass between the cells, and there is a possibility of the intercellular cement forming a route for absorption.

Generally speaking, therefore, absorption is an active or vital process, even in the case of water and salts, but it may be assisted or retarded by the physical processes of diffusion and osmosis.

THE ABSORPTION OF THE PRODUCTS OF THE DIGESTION OF PROTEINS.—The proteins of the food are almost entirely hydrolysed into amino-acids before being absorbed, but the final stages of the digestive process may be effected by means of erepsin actually in the mucous membrane of the intestine after absorption has begun. Even coagulable proteins may be taken up by the epithelial cells. It has been shown that an animal can absorb its own serum, and this will take place when the intestine has been washed free of enzymes. Similarly egg-albumin may be absorbed,

the amount introduced into the bowel in one experiment being reduced by one-fifth in three hours. It is probable that, even in these circumstances, complete digestive hydrolysis takes place in the mucous membrane, and that all the proteins of the food are hydrolysed to amino-acids before they enter the blood-stream.

It is probable that some of the products of the digestion of protein are synthesised into protein in the walls of the villi. This would account for the great increase in the size of the epithelial cells of the villi during protein absorption. The synthesis occurs chiefly at the basal ends of the cells where a marked accumulation of coagulable material takes place. There is no doubt, however, that the bulk of the amino-acids enter the blood-stream as such, and their presence in the circulating blood can be demonstrated by the following means:—

An artery of an anæsthetised animal is connected with one end of a series of tubes the walls of which consist of a thin collodion membrane, the other end of the series being attached to a vein. The system of tubes (Fig. 164) is filled with saline solution, and hirudin is injected into the animal; the blood is then allowed to flow from the artery through the tubes and back to the vein, a continuous circulation of the animal's blood being thus maintained. The tubes are surrounded by normal saline solution at the temperature of the body, and, as the blood flows through them, its diffusible constituents, including sugar and amino-acids, pass through the collodion wall into the saline solution, and can be subsequently estimated. Since amino-acids diffuse into the salt solution, they must have been previously present in the circulating blood.

Further, the percentage of amino-acids in the circulating blood has been estimated by chemical methods, and has been found to increase after a protein meal.

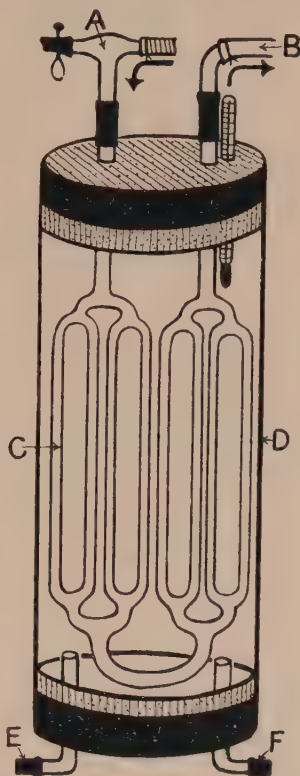


FIG. 164.—Diffusion apparatus. (Semi-diagrammatic.)

A, arterial cannula; B, vein; C, collodion tube; D, outer vessel containing saline solution; E, F, tubes for admitting or removing saline solution.

THE ABSORPTION OF THE MONO-SACCHARIDES.—The products of carbohydrate digestion all belong to the group of mono-saccharides and are easily diffusible substances. The chief of these is glucose, but some fructose is formed by the hydrolysis of cane-sugar, and some galactose by that of the sugar of milk. All three varieties are absorbed directly into the blood-stream. During absorption of a carbohydrate meal more sugar is found in the portal vein than in the hepatic vein. Moreover, the absorption of sugar is not accompanied by an increase of that substance in the lymph of the thoracic duct, and it is not interfered with by ligation of that structure. Di-saccharides are not absorbed from the intestine.

THE ABSORPTION OF FAT.—The products of digestion of fat are fatty acid, held in solution by the bile-salts, glycerol, and a little soap. The absorption of fat differs from that of amino-acids and glucose in that it takes place for the most part into the lymphatic system. During the absorption of a fatty meal, the lymphatics of the mesentery become filled with a milky fluid called *chyle*, so that they are easily visible to the naked eye. Chyle collected from the thoracic duct may contain over 6 per cent. of fat. The absorbed fat reaches the blood-stream by the thoracic duct, and, if an animal be bled during absorption of fat, the plasma will be found to be milky from the quantity of minute fat-globules present in it. A few hours later the plasma is again clear, because the small quantity of fat still present in it is held adsorbed by the serum-proteins, the remainder having been either oxidised or transferred to the fat-depôts of the body.

About 98 per cent. of the fat taken as food is absorbed, but only 60 per cent. can be recovered in the chyle. With regard to the 38 per cent. which remains to be accounted for, some of it is converted into lecithin, some into cholesterol, and some remains in the form of soap. Some of each of these substances is carried in the corpuscles and the rest in the plasma.

The bile-salts have an important influence on the absorption of fat, partly because of their property of holding fatty acids in solution, and partly because they reduce surface tension and so facilitate the passage of the fatty material into the epithelial cells. In the absence of bile 60 per cent. of the fat of a meal remains unabsorbed. The pancreatic juice also aids the absorption of much of the fat, because fat is not absorbed so rapidly in the absence of lipase.

The soaps formed in the intestine are split up by the intestinal epithelial cells into fatty acids and alkali. The fatty acids are absorbed, and recombined with glycerol in the cells to form

neutral fats. Thus the epithelial cells covering the villi become filled with droplets of fat, which may be stained black with osmic acid (Fig. 165), orange with Scharlach R or Sudan III, or pink by means of Nile-blue. The reaction with Nile-blue shows that the droplets consist of neutral fat, proving that a re-synthesis has taken place in the epithelial cells. The fat may be traced through the cells into the core of the villi, where the droplets are finely emulsified by the lymph in the tissue-spaces, and are carried into the central lacteals.

Alternate contraction and relaxation of the muscular fibres in the villus tend to propel the contents of the central lacteal towards the larger lymphatic vessels in the intestinal submucosa.

It has been demonstrated that hydrocarbons such as paraffin and petroleum are not absorbed in the intestine, and that they greatly slow the rate of absorption of the foodstuffs.

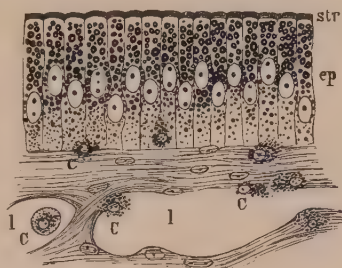


FIG. 165.—Mucous membrane of frog's intestine during absorption of fat. (From Schafer's *Essentials of Histology*.)

ep, epithelium: str, striated border
c, leucocytes; l, lacteal.

SECTION VII

THE LARGE INTESTINE.—Four or five hours after each meal the contents of the small intestine begin to pass through the ileo-colic junction into the large intestine. An important factor in promoting the transference of material from ileum to colon is the gastro-ileac reflex. The entrance of the succeeding meal into the stomach excites the production of peristaltic waves in the lower part of the ileum, and, as each wave reaches the ileo-colic junction, the sphincter is relaxed. In this way the contents of the ileum are propelled into the colon in successive portions, and if they contain bismuth the level which they attain in the ascending portion of the large intestine can be observed by means of X-rays to rise towards the hepatic flexure in an intermittent manner.

The material which passes into the bowel is in the form of a jelly, coloured by the presence of bile-pigment. It normally contains hardly any nutritive substances, the derivatives of the digestion of protein, fat, and carbohydrate having been almost completely absorbed in the small intestine. Indigestible substances contained in the food are present, especially cellulose,

together with cast-off epithelial cells and the dead bodies of bacteria. The chief secretory waste products are the pigment of the bile, unabsorbed glycocholate and taurocholate of sodium, and cholesterol.

THE FUNCTIONS OF THE LARGE INTESTINE.—In carnivorous animals the large intestine is relatively short, and its function is almost entirely limited to the absorption of water and the consequent reduction in bulk of the fæces. In herbivora, on the contrary, the large intestine is of considerable length, and not only absorbs water but serves an additional purpose. A large proportion of vegetable foodstuffs consists of cellulose, which is not affected by the digestive enzymes. Cellulose is decomposed in the large intestine of the herbivora by bacterial action, being converted into fatty acids, which are absorbed and utilised in the body. Further, in all the higher animals, the cells lining the simple tubular glands of the large intestine are for the most part of the mucus-secreting type, and are of service in producing mucin, which acts as a lubricant and facilitates the passage of the fæces along the bowel.

In man the functions of the large intestine include secretion, excretion, and absorption, and in addition some bacterial decomposition takes place in its contents.

(1) The *secreted* material, as in the higher animals generally, is mucin, derived from the tubular glands of the mucous membrane.

(2) The substances *excreted* by the large intestine are calcium, magnesium, and iron, chiefly in the form of phosphates. The amount of calcium excreted by the bowel varies inversely with the amount contained in the urine. Acid urine, such as occurs normally in carnivora, and in man when the diet contains a due proportion of protein, holds calcium phosphates in solution, and in such a case the proportion of calcium excreted by the large intestine is small. When the urine is alkaline, as in herbivora, and in man when the diet is largely vegetable, the amount of calcium excreted by the bowel is greater. Other chemical substances taken as drugs—for example, mercury—may also be excreted by the large intestine.

(3) The only substance *absorbed* in any quantity in the large bowel is water. The contents of the ascending colon are free of nutritive substances, but their bulk is fairly large owing to the amount of fluid which they contain. During their stay in the large intestine the bulk is greatly reduced, chiefly by the absorption of water; it is said that 400 c.c. of water are absorbed from the contents of the colon in twenty-four hours. The possibility

of the absorption of nutritive substances in the large intestine is of importance, because attempts are frequently made to introduce foodstuffs into the body by means of rectal injections. Experiments prove, however, that nutritive material is not absorbed by the large intestine, with the exception of glucose, and this only in small amounts. But some injected material may find its way through the ileo-cæcal opening into the small intestine, and be absorbed there.

(4) The *bacteria* in the human large intestine act upon cellulose with the production of lower fatty acids, marsh gas (CH_4), carbon dioxide, and hydrogen. The fatty acids are then absorbed. Undigested protein residues also undergo bacterial decomposition, with the production of certain amines and the aromatic bodies, indole ($\text{C}_8\text{H}_7\text{N}$), skatole (methyl-indole), and phenol; if these are absorbed they travel with the portal blood to the liver. This organ detoxicates them, changing them into ethereal sulphates. They then travel by the blood to the kidney to be excreted in the urine. (See Chapter XXI).

SECTION VIII

THE MOVEMENTS OF THE LARGE INTESTINE.—The movements of the large intestine have been most satisfactorily studied with the aid of X-rays (Fig. 166).¹ The cæcum and ascending colon are filled, in the manner which has already been described (p. 389), by the peristaltic contractions of the ileum, and are entirely passive during the process.

ANTIPERISTALSIS.—In animals, rings of constriction appear near the junction of the ascending and transverse colon, and pass backwards along the ascending colon to the cæcum; regurgitation of the contents of the colon into the ileum is prevented by closure of the ileo-colic sphincter. These movements, which are known as *antiperistalsis*, serve to churn up the contents of the colon and to assist the absorption of water. They are not preceded by relaxation of the intestinal wall. Antiperistalsis occasionally occurs in man.

PERISTALSIS.—The transference of the contents of the cæcum and ascending colon to the transverse and descending colon takes place at long intervals, usually three or four times in twenty-four hours, by means of rapid peristaltic contractions. These movements generally follow the entry of food into the

¹ We are indebted for this diagram to the kindness of the Oxford University Press.

stomach, and are ascribed to a gastro-colic reflex. Scattered masses may remain in the transverse colon for a time, and these are gradually transferred to the descending colon by a slow peristaltic wave.



FIG. 166.—Passage of food along the large intestine after a bismuth meal, as seen by means of X-rays. The numbers refer to the hours after the meal was taken. (Hertz.)

The faeces remain for a time in the sigmoid flexure, until, usually after a meal, a certain amount passes into the rectum and gives rise to the desire for defæcation. By relaxation of the sphincter ani, accompanied by contraction of the walls of the sigmoid flexure and rectum, and assisted by voluntary contraction of the muscles of the abdominal wall and pelvic floor,

the lower end of the bowel is evacuated. The act is a reflex one, but in the adult it is under the control of the higher centres.

THE NERVE-SUPPLY OF THE LARGE INTESTINE.—The large intestine receives its nerve-supply from the sympathetic system and from the pelvic visceral nerves or *nervi erigentes* (Fig. 128). The sympathetic fibres form the inferior mesenteric nerves, running from the inferior mesenteric ganglion to the ascending, middle and transverse colon, and the hypogastric nerves pass from the same ganglion to the rectum. The pre-ganglionic fibres emerge from the spinal cord by the first, second, and third anterior lumbar nerve-roots.

The pelvic visceral nerves emerge from the cord by the second and third sacral nerve-roots, and are distributed to the whole length of the large intestine. Stimulation of the sympathetic nerves causes inhibition of the tone of the intestinal wall and cessation of its movements. Stimulation of the pelvic nerves causes contraction of the whole length of the colon. The sympathetic is therefore inhibitory, and the pelvic visceral nerves are motor in function.

As in the small intestine, there are ganglionated plexuses in the wall of the large intestine, of which the myenteric, lying between the layers of the muscular coat, is associated with the local reflex mechanism controlling the movements of the bowel.

THE VERMIFORM APPENDIX.—In man the cæcum is very short and has attached to it a wormlike process, the vermiform appendix. This has a thin muscular coat and a thicker mucous coat, the latter composed of lymphoid tissue containing scattered Lieberkühn's glands. The human appendix is regarded as a vestigial remnant of no functional importance.

THE FÆCES.—The residues which finally reach the rectum constitute the fæces, and form a solid or semi-solid mass, coloured by the pigment stercobilin, which is derived from bilirubin. They contain about 65 per cent. of water, with organic material and inorganic salts. The organic substances are partly nitrogenous and partly of a fatty nature, and soluble in ether. They include cholalic acid, dyslysin, indole and skatole, purine bodies, epithelial cells, and dead bacteria. The lipoids are fatty acids, lecithin, and coprosterol, a body allied to cholesterol. There may be a small quantity of neutral fat. When vegetable food has been taken, the fæcal matter will include undecomposed cellulose, but for the most part the fæces consist of substances derived from the digestive tract itself.

CHAPTER XVI

MATERIAL METABOLISM

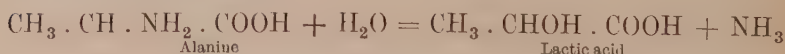
SECTION I

WE have seen that as the result of digestion various breakdown products are formed from the diet. These are briefly amino-acids and nucleic acids, fatty acids, and glycerine, hexoses and pentoses and thioses, in which form they enter the bowel wall.

In the urine we find excreted urea, ammonia, and creatinine, uric and hippuric acids, phosphates and sulphates. In addition, CO_2 in large volumes leaves the lungs. It is the object of this chapter to shed some light on the connections between the substances which are ingested and those which are excreted.

THE DEAMINATION OF PROTEIN.—It has been pointed out (p. 387) that the products of the digestion of protein are absorbed into the blood-stream almost entirely as amino-acids. They are then taken up from the blood, partly by the muscles and other tissues, for making good wear and tear, partly by the liver where they rapidly undergo *deamination*.

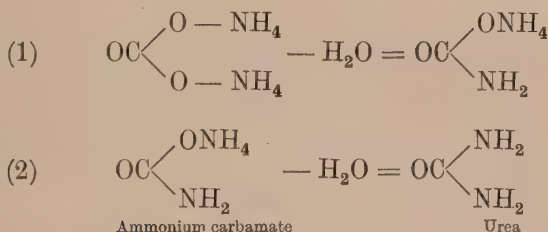
Deamination.—This consists in the removal of the amino-group, and its replacement either by oxygen or by a hydroxyl radical. A simple illustration of this change is represented in the following equation :—



The amino-acids are thus converted into either oxy- or keto-acids, which on reduction become ordinary fatty acids. This change is probably brought about by an enzyme. It takes place chiefly in the liver and to a smaller extent in other tissues. Its occurrence in the liver is proved by the observation that, when amino-acids are added to pounded liver-substance under aseptic conditions, the amount of ammonia rapidly increases. The removal of the amino-group does not appreciably diminish the calorie-value of amino-acids, or their usefulness as a source of

energy to the body. Thus 89 grammes (1 gram-molecule) of alanine, when fully oxidised, give out 389 calories; if its amino-group is replaced by hydroxyl, alanine is converted into 90 grammes (1 gram-molecule) of lactic acid, which, if completely oxidised, would yield 329 calories. In the course of the digestion of protein some ammonia is set free in the small intestine as a result of deamination. This is absorbed by the villi, and carried in the portal circulation to the liver.

FORMATION OF UREA.—The ammonia set free by deamination is carried to the liver, and, together with that similarly formed in the liver itself, is converted into urea. The ammonia set free enters into combination with carbon dioxide to form ammonium carbonate. This with the loss of one molecule of water becomes ammonium carbamate, which in its turn loses a further molecule of water to form urea, thus:—



The formation of urea in the liver has been proved in several ways. In the first place, when the liver of a recently killed animal is removed from the body and perfused with oxygenated blood to which ammonium carbonate or carbamate is added, the ammonium salt disappears from the blood, being replaced by urea; this change does not occur when blood containing ammonium salts is perfused through other organs.

For further details of the deamination of proteins see Chapter XX.

AMMONIA EXCRETION.—In normal circumstances the quantity of ammonia which appears as ammonium salts in the urine is small, usually under 1 gramme. If, however, the blood becomes acid ammonium salts are excreted in greatly increased amounts, and there is a corresponding diminution in the urea excretion. Under these conditions it was thought that the liver failed to convert some of the ammonium carbonate (resulting from deamination) into urea, but recent evidence shows that the ammonium salts are formed by the kidney cells out of part of the urea brought to them by the blood from the liver.

NITROGEN EXCRETION.—When the composition of the urine excreted in twenty-four hours by a man taking little protein food is compared with that of the same person when taking an abundance of protein food, great differences are observed, and are shown in the following table (Folin) :—

	Abundant Protein Diet.	Percentage of Total Nitrogen.	Low Protein Diet.	Percentage of Total Nitrogen.
Quantity of urine .	1170 c.c.	...	385 c.c.	...
Total nitrogen .	16·8 grms.	...	3·6 grms.	...
Urea N .	14·7 "	87·5	2·2 "	61·7
Ammonia N .	0·49 "	3·0	0·42 "	11·3
Uric acid N .	0·18 "	1·1	0·09 "	2·5
Creatinine .	0·58 "	3·6	0·60 "	17·2
Total SO ₄ .	3·64 "	...	0·76 "	...
Inorganic SO ₄ .	3·27 "	...	0·46 "	...
Ethereal SO ₄ .	0·19 "	...	0·10 "	...

The urea and sulphates in the urine are greatly increased by a protein meal, whereas the creatinine is but little affected, this difference being due to the fact that the metabolism of protein in the body is of two kinds, *endogenous* and *exogenous*. By endogenous metabolism is meant that occurring to the proteins of the man's own body as the result of wear and tear. By exogenous metabolism is meant that occurring to the proteins of the man's diet.

EXOGENOUS METABOLISM.—The amount of urea and inorganic sulphates in the urine depends chiefly upon the quantity of protein in the food, the urea being formed mainly from ammonia set free by the deamination of the amino-acids absorbed into the blood-stream during digestion. The sulphur of the inorganic sulphates is derived from the sulphur present in protein which is split off and oxidised without being built up into the tissues. The formation of urea and sulphates thus represents a change in the amino-acids which takes place before they undergo metabolism in the muscles and other tissues, and which is independent of the metabolic changes in the tissues themselves. For this reason, the formation of urea and sulphates is described as exogenous metabolism. But some urea is also derived from the breaking down of the proteins of the tissues themselves, and is therefore endogenous in origin; and the whole of the urea appearing in the urine during starvation is formed from tissue-protein.

The correctness of this view is proved by the rapidity with which urea is excreted in the urine after a protein meal; the excretion of urea begins to increase within two hours after the

meal, and, within five hours, half the total nitrogen taken in with the food may be excreted as urea. It would be almost impossible for the body to have built up the amino-acids into the living tissues, and to have broken them down into urea within so short a time. The amount of urea in urine, therefore, serves as an index of the quantity of protein taken in the food; and the removal of ammonia from amino-acid, and its rapid excretion as urea, furnishes a means by which the body rids itself of nitrogen which is not needed, while retaining the resulting oxy-acids as a source of energy.

ENDOGENOUS METABOLISM.—The amino-acids formed during the digestion of protein serve two purposes in the body.

(1) The greater part of the amino-acids, after being deaminated, is carried to the tissues and oxidised to carbon dioxide and water, thereby serving as a source of energy. In this respect protein has no advantage over other foodstuffs as a source of energy, since the amino-acids are converted by the removal of their amino-group into fatty acids.

(2) A certain proportion of the amino-acids is built up in the tissues into living substance to replace that which is constantly being broken down. The proteins in the tissues of different animals and of different tissues in the same animal vary in composition; and the synthesis in each tissue of its characteristic proteins is made possible by the previous disintegration of the proteins in the food into their ultimate constituents, namely, amino-acids. These acids are often spoken of, therefore, as "building-stones" which can be put together in varying combinations in the building up of different proteins present in the tissues of the body. Convincing proof that the tissue-proteins are synthesised from amino-acids is furnished by the following experiment. If an animal receives as its sole nitrogenous food the mixture of amino-acids formed by the prolonged pancreatic digestion of casein, with the addition of fat, carbohydrate, salts, and water, it remains in good health and may gain weight.

ESSENTIAL PROTEINS.—Hopkins has by feeding experiments investigated the part played by individual amino-acids in the building up of protein, and has shown that animals fed on the diet described above, but with tryptophane absent from the mixture of amino-acids, rapidly lose weight and die. Hence tryptophane is essential for the synthesis of the tissue-proteins. If only glutamic and aspartic acid are absent from the diet, the animals remain well and gain weight.

Experiments of this kind make it clear that the amino-acids

fall into two groups. (1) One group, which includes tryptophane, tyrosine, phenyl-alanine, arginine, histidine, and cystine, is essential for the building up of the tissues and therefore for life; these compounds cannot be produced in the body and must be supplied in the food. Substances which are deficient in one or more of these groupings cannot act as tissue-builders in the body and therefore cannot maintain life. Thus, zein, which is a protein in maize, contains neither tryptophane nor lysine, and young animals fed on zein, with the addition of fat, carbohydrate, salts, and water, rapidly lose weight, and die after a short time. The disease pellagra,¹ seen in maize-eating peoples, is believed to be due to lack of these essential amino-acids in zein. Animals fed on the same diet, with the addition of tryptophane, remain well

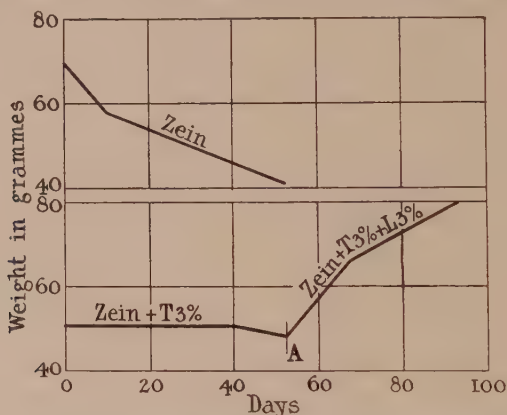


FIG. 167.—Chart showing the effect of different diets on the weight of young rats. (After Osborne and Mendel.)

T = tryptophane; L = lysine.

and maintain their weight; and if lysine, as well as tryptophane, is added to the diet, normal growth occurs (Fig. 167). It has also been observed that young animals fail to grow when their sole protein food is gliadin, which contains no lysine, although adult animals can maintain their weight on this diet. Lysine appears, therefore, to be essential for growth, but not for the maintenance of the body. Further, some of the amino-acids seem to be necessary for the production of definite substances in the body; thus adrenaline and thyroxin are both formed from tyrosine.

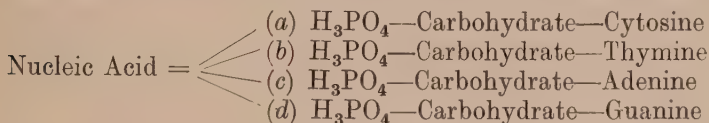
(2) The other group, including most of the other amino-acids, is not essential to life, and is used in the body chiefly as a source of energy. If these acids are not supplied in the food, some of

¹ See, however, page 428.

them—for example—glycine, can be formed by the tissues, probably from ammonia and carbohydrate derivatives. Further, in the course of their metabolism in the tissues, the amino-acids stimulate metabolism as a whole and largely increase the production of heat in the body; this influence is called the *specific dynamic action* of protein. Comparatively little is known of the intermediate stages in the breaking down of protein in the tissues, though the composition of the urine during starvation shows that the end-products include urea, uric acid, and creatinine.

SECTION II

PURINE METABOLISM.—The nucleo-proteins of the food are broken down in the digestive tract into nuclein and protein, the nuclein subsequently undergoing further digestion with the setting free of nucleic acid. This in its turn is broken up thus:—

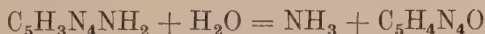


(Carbohydrate is pentose in case of plants and hexose in case of animals. Nucleoside = Carbohydrate—Purin or Pyrimidine. Nucleotide = H_3PO_4 —Carbohydrate—Purin or Pyrimidine.)

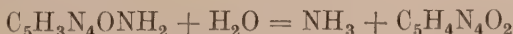
(a) and (b) both consist of phosphoric acid and hexose (or pentose if vegetable) and pyrimidine. They enter the blood in this form.

(c) contains adenine instead of pyrimidine.

(d) contains guanine. Both (c) and (d) are split up into their constituent radicals:• Phosphoric acid—carbohydrate and purine base. The two former enter the blood, the phosphoric acid to go to the kidney for excretion, the carbohydrate to provide energy for the tissues. The purine bases are acted on by enzymes in the intestinal wall and in the liver. Adenine by deamination becomes hypoxanthine, thus:—



The latter is then acted on by oxidases and is finally converted into uric acid ($\text{C}_5\text{H}_4\text{N}_4\text{O}_3$). Guanine by deamination becomes xanthine, thus:—



and this is then also oxidised to uric acid.

In man, uric acid is thus one end-product of the action of these enzymes on nucleic acid.

The amount of uric acid appearing in the urine does not represent the whole of that formed from the nucleo-proteins of the food, but is derived partly from them, forming exogenous uric acid, and partly from the breaking down of the nucleins in the tissues, endogenous uric acid. It will be seen from the table on p. 396 that, as a rule, half the uric acid in the urine is of endogenous, and half is of exogenous, origin.

When the diet is free from nucleo-protein, the excretion of endogenous uric acid is relatively constant, but it depends on the adequacy and character of the diet, and is increased after severe muscular exercise, and also in fever, owing to a greater breaking down of the nuclei in the cells of the body.

The exogenous fraction varies in amount with the character of the diet, being absent when this contains no nucleo-protein, and increased by foods such as kidney, sweetbread, and liver, which are rich either in nucleo-protein or in the precursors of uric acid, such as hypoxanthine.

Normally the nucleins broken down in the wear and tear of the tissues are probably replaced by the synthesis of fresh nucleo-protein from the purine material taken in the food. If the diet is free from nucleo-protein, this endogenous purine must be manufactured in the body from amino-acids. In the growing infant, nucleo-protein is rapidly being laid down in the body, although the food (milk) contains hardly any nucleo-protein.

SECTION III

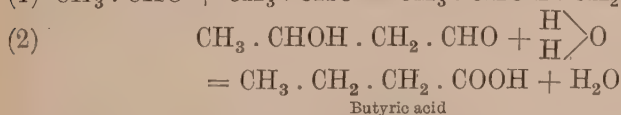
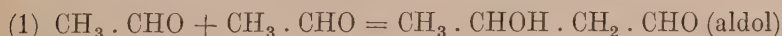
THE METABOLISM OF FAT.—About 60 per cent. of the fats taken by the mouth, after being hydrolysed in the digestive tract and re-synthesised in the walls of the villi, enter the thoracic duct as neutral fats and pass into the blood-stream. Of the remaining 40 per cent. the greater part appears to enter the blood-stream direct, through the wall of the villi. It is carried by the leucocytes, red cells and plasma, partly as fats, partly as soaps, and partly as lipoids. The latter seem to be formed in the bowel wall from phosphoric acid, chlorine, glycerol and fatty acids. For a short time after a fatty meal the fats circulate in the blood-stream, and may give the blood a slightly milky appearance. The blood fat begins to mix about an hour after a meal and reaches the maximum six hours after the meal. The fats are, for the most part, rapidly taken up from the blood and stored in the subcutaneous tissues and omentum, which serve as depôts in which the fat not immediately required by the body can be kept. The composition of the subcutaneous fat thus reflects that of

the fat in the food ; except that it contains a higher percentage of unsaturated fats. If abnormal and easily recognisable fats are given by the mouth, they can be identified shortly afterwards in the fat in the subcutaneous tissue. For this purpose, erucic acid or fats containing iodine may be used.

PRODUCTION OF FATS FROM CARBOHYDRATES.—In man the greater part of the fat deposited in the body is derived from the fat in food, but it can be formed, and in herbivora is mainly formed, from carbohydrates. This was demonstrated in the classical experiment of Lawes and Gilbert. These observers took two young pigs from the same litter. One was killed, and the amount of fat and protein in its body was determined ; the other was fed on a diet containing known quantities of protein, fat, and carbohydrate, and after some weeks it was killed and the amount of fat in its body was ascertained. After deducting the amount of fat taken in the food from that present in the animal's body when it was killed, a large residue remained, which must have been formed from either the protein or carbohydrate of the food. It could not have been formed from protein, since the amount of fat in the animal was larger than the amount of protein food consumed. The greater part of the fat must, therefore, have been formed from carbohydrate ; and there is no doubt that in herbivora, whose diet consists mainly of carbohydrate, the bulk of the fat is formed in this way. There is no evidence that fat can be formed from protein, and animals, *e.g.* dogs, fed on a purely protein diet do not put on any fat.

The process by which carbohydrate is converted into fat in the body is not known, but it is probable that the carbohydrate is first broken down into pyruvic acid ($\text{CH}_3\text{CO}\cdot\text{COOH}$), which, by decarboxylation, yields acetic aldehyde ($\text{CH}_3\cdot\text{CHO}$), and that, by the linking up of molecules of the latter, the fatty acids are synthesised.

Their possible formation from aldol is thus shown :—



The fat formed from carbohydrate contains a larger proportion of stearin and palmitin, and has a higher melting-point than that usually deposited in the tissues from the food. For this reason the fat of cattle is much firmer than that of omnivorous animals, which may be practically fluid at the temperature of the body.

DESATURATION OF FATS.—The fat in the fat-depôts cannot be used directly by the muscles or other tissues, but has first to undergo certain changes in the liver; these consist in the conversion of saturated into unsaturated fats by the removal of hydrogen. A saturated fat, *e.g.* stearin, is one in which the affinities of all the carbon atoms are satisfied, whereas an unsaturated fat, such as olein, is one in which the affinities of two or more of the carbon atoms are unsatisfied and the carbon atoms are united by a double bond. Thus oleic acid has the formula $C_8H_{17} \cdot CH : CH \cdot C_7H_{14} \cdot COOH$, and has one double bond.

The fatty acids present in the liver contain two, three, or even four double bonds, each of which represents a weak spot in the long chain of carbon atoms; and an unsaturated fatty acid tends to split at these points with the formation of smaller molecules. The less complex fatty acids formed by the liver are carried to the muscles and other tissues, in which they enter the protoplasm of the living cells, and are finally oxidised to carbon dioxide and water.

During starvation the fat in the body is used by the tissues as their chief source of energy, and the liver is called upon to desaturate fat in larger amount and thus render it available for use by the tissues. The liver takes up more fat from the blood, and, at the same time, fat passes in larger amount from the fat-depôts into the blood. The fat passes to the liver from the fat-depôts more rapidly than it can be desaturated, and an accumulation of saturated fat takes place in the liver. This accumulation, which is termed *fatty infiltration*, readily occurs in starvation, and equally readily passes off again when food is given. It takes place not only in starvation, but whenever the tissues need a larger supply of fat, for example in diabetes, and usually occurs only when the liver-cells are free or almost free from glycogen.

The nature of the process whereby the subcutaneous tissues and omentum take up fat after a meal and give it off to the blood again in times of need is not known, though it has been supposed to be due to the reversible action of an enzyme (lipase) in the fat-cells.

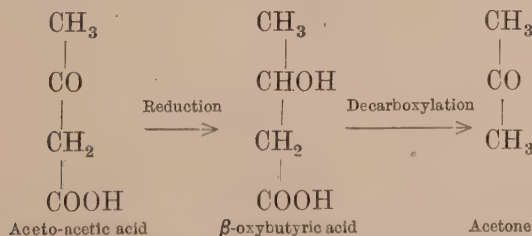
In a man whose weight remains steady the fat taken in the food is rapidly used in supplying energy in the body, and little or none of it is permanently stored in the fat-depôts. When weight is being put on, a certain proportion of fat in the food is stored up instead of being oxidised, and fats also may be formed from carbohydrate. On the contrary, loss of weight during starvation, or produced by some other means, involves depletion of the store of fat in the body. The fat normally stored represents

a reserve of potential energy which can be increased, or which, in time of need, can be drawn upon for the use of the muscles and other tissues ; and the calorie-value of fat is so high that the energy which may be thus kept in reserve is very considerable.

INTRACELLULAR FAT.—The fats in the tissues are combined in such a way that they can no longer be recognised histologically, although their presence is made manifest by chemical analysis of the tissue. A healthy kidney, for instance, when stained with Sudan III, may show only a few specks of fat here and there, although, when analysed, it is found that 18 to 20 per cent. of its dried substance is fat. Under the influence of certain poisons (*e.g.* phosphorus), and in some diseases, the combination of fat with the rest of the protoplasm is broken, and the fat is set free in such a form that it can be stained and recognised under the microscope. This change, which is called *fatty degeneration*, was formerly believed to be the result of the formation of fat from protein. Chemical analysis of such an organ shows, however, that it contains no more fat than would be found in a healthy organ. Hence fatty degeneration implies, not the formation of fat from protein, but merely the setting free, in a visible form, of previously combined fat.

THE OXIDATION OF FATS.—When fat is oxidised in the tissues, the final products are carbon dioxide and water ; in all probability the long chain of carbon atoms constituting a fatty acid is broken down in stages, either two or four carbon atoms being split off at each stage, and converted into carbon dioxide. The complete oxidation of fat, however, is dependent upon the presence of carbohydrate in the tissue-cells.

When the tissues are deprived of carbohydrate—for example, during starvation or on a diet free from carbohydrate—the oxidation of fat is incomplete, and intermediate metabolic products are formed in the tissues and pass into the blood and urine. These products are aceto-acetic acid, β -oxybutyric acid, and acetone, their chemical relationship being shown as follows :—



In all probability aceto-acetic acid and β -oxybutyric acid are normally formed in the body during the metabolism of fat, but are fully oxidised. In the absence of carbohydrate they pass into the blood-stream, and aceto-acetic acid and β -oxybutyric acid, instead of undergoing oxidation, accumulate in the blood, and are excreted in the urine. After the urine has been passed, some of its aceto-acetic acid is converted into acetone. The origin of these bodies from fat is clearly shown by experiment. For when the diet consists solely of fat, their amount in the urine may become very large. Further, there is evidence that aceto-acetic acid can also be formed from amino-acids, notably from leucine and tyrosine. β -oxybutyric acid and its products are formed, to some extent at least, in the liver. The presence of these substances in the urine is an indication that the supply of carbohydrate to the tissues is inadequate. When β -oxybutyric and aceto-acetic acids are present in the blood in appreciable amount, they combine with ammonia which would otherwise be converted into urea. They also react with sodium bicarbonate in the blood-plasma, thereby reducing the "alkali-reserve."

Test for Aceto-acetic Acid in Urine.—On adding a solution of ferric chloride, in excess of that required to precipitate the phosphates, the appearance of a deep red colour indicates the presence of aceto-acetic acid. This test is not given by acetone.

Since carbohydrate is readily converted into fat in the body, it might be expected that the converse change would also occur. Such a possibility is indicated by the fact that in hibernating animals the respiratory quotient is low, and may fall even to 0.3. A quotient of this size could occur if fat were being transformed into glucose, since, in such a process, much of the oxygen taken into the body would not reappear as carbon dioxide.

SECTION IV

THE METABOLISM OF CARBOHYDRATE.—To ensure efficient working of the muscles it is essential that there should be a constant supply of carbohydrates in the blood. If, however, an excess occurred, osmotic phenomena would be brought into play, and this must be guarded against. The carbohydrates are absorbed from the digestive tract and enter the blood-stream mainly as glucose. The arterial blood contains free glucose in an amount which varies slightly according to the state of carbohydrate digestion, but never falls below 0.08 per cent. or rises above 0.2 per cent. in normal individuals, in the extremes between starvation and the ingestion of 200 grammes of sugar at one meal.

In order to demonstrate or estimate the glucose in blood, the proteins must be first precipitated (*e.g.* by colloidal iron); the

glucose can then be estimated by an appropriate method in the filtrate.

In normal fasting individuals the blood-sugar content (usually estimated in venous blood) is about 0.1 per cent. If 50 grammes of glucose be now given by the mouth, the blood-sugar rises to a maximum of about 0.18 per cent. in about thirty minutes, and falls again to the fasting level in one to two hours (normal blood-sugar curve). The sugar in the portal blood, in experiments on animals, shows greater fluctuations than that in general circulation, being slightly less than the latter during starvation, and distinctly greater after a carbohydrate meal; and it is clear that the sugar absorbed during digestion undergoes some change as the blood passes through the liver. This change consists in the conversion of sugar into *glycogen*, which is stored in the liver-cells.

Claude Bernard, who discovered glycogen, concluded, first, that the sugar absorbed from the digestive tract entered the portal blood, and that the liver removed the sugar from the blood and stored it as glycogen. Second, that the percentage of sugar in the systemic blood normally remained nearly constant, and that, as the sugar was removed from the blood by the tissues for their metabolism, some glycogen was converted into sugar by the liver; this passed into the general blood-stream, thereby keeping the percentage of sugar in arterial blood at the normal level. The rapid conversion of glycogen into sugar after death was due to a ferment the activity of which was no longer controlled as it had been during the life of the animal. Glycogen may thus be regarded as a store of carbohydrate which is increased at each meal, and which is continuously being drawn upon by the tissues. In all probability the conversion of sugar into glycogen, as of glycogen into sugar, is carried out by an enzyme which has a reversible action. We may perhaps regard glucose as the body's "cash in hand," glycogen as a sort of "current account," which fluctuates from day to day, and the store of fat as "invested capital," which can be called upon in times of stress. Although the main source of glycogen is carbohydrate food, it can also be formed from protein, since, when an animal is starved until its liver is presumably free from glycogen and is then killed shortly after a large meal of protein, glycogen is found in its liver. There is no evidence that glycogen can be formed from fat. Glycogen is found most abundantly in the liver, but it occurs in muscles and in the white blood-corpuscles.

FATE OF SUGAR.—The carbohydrate taken into the body ultimately undergoes one of two changes. Some of it may be converted into fat; the remainder passes from the blood to the tissues, where it is oxidised and used as a source of energy. There

is direct evidence that sugar is made use of by the tissues. In the heart-lung preparation (p. 110) the normal heart uses up sugar at the rate of about 4 milligrams per gramme of heart per hour. Further indirect evidence to the same effect is furnished by the fact that the glycogen disappears most rapidly from the liver when the functional activity of the tissues is greatest. Thus severe muscular exercise or the convulsions induced by strychnine lead to the rapid diminution of the amount of glycogen in the liver. It is probable that hexose phosphate (lactacidogen) and lactic acid are intermediate products in the conversion of sugar into carbon dioxide and water.

Some light is thrown on the conditions which influence the setting free of glucose from the liver and its further oxidations in the tissues by abnormal conditions in which glucose appears in the urine, and which are known as glycosuria.

GLYCOSURIA.—The urine normally contains only minute traces of glucose, and does not reduce Fehling's solution; the term glycosuria is only used when the urine contains glucose in sufficient amount definitely to reduce such a solution. This may occur in a variety of circumstances. If glucose is injected into the circulation or under the skin, the percentage in the blood rises (hyperglycæmia), and the sugar is at once excreted by the kidneys as soon as its concentration in the blood reaches 0·19 per cent. A similar condition, known as *alimentary glycosuria*, is observed when very large amounts of glucose (more than 200 grammes) are taken by the mouth. The ingestion of starch, even in large quantities, does not lead to glycosuria, since its digestion and absorption are sufficiently slow to allow the liver to convert the sugar into glycogen.

ADRENALINE GLYCOSURIA.—The injection of a small quantity of adrenaline into the circulation is often followed by the appearance of glucose in the urine; at the same time glycogen disappears from the liver, and the percentage of sugar in the blood is increased. Evidently the adrenaline causes the liver to discharge its glycogen into the blood as glucose, which is excreted by the kidneys. Glycosuria may also occur under any conditions in which adrenaline is set free into the blood-stream in larger amount from the suprarenal glands. For example, it may follow stimulation of a splanchnic nerve or puncture of the floor of the fourth ventricle (puncture diabetes).

PHLORIDZIN GLYCOSURIA.—Phloridzin is a glucoside which, on hydrolysis, yields glucose and phloretin. A small amount of phloridzin or phloretin, when injected into an animal, produces glycosuria and the disappearance of glycogen from the

liver; but phloridzin glycosuria differs from those just described in that the percentage of sugar in the blood is not increased, but tends rather to be diminished. Phloridzin acts upon the kidneys, as may be shown by collecting the urine separately from the two kidneys, and injecting a small dose of phloridzin into one, *e.g.* the right, renal artery; the urine flowing from the right kidney is then found to contain sugar five to eight minutes before it appears in the urine from the opposite kidney. The drug appears to act directly upon the cells of the renal tubules, and this view is supported by the observation that the repeated administration of phloridzin produces definite histological changes in the cells of the renal tubules. The sugar in this case is not derived from carbohydrate, but is formed from protein.

EXPERIMENTAL DIABETES.—The complete removal of the pancreas in dogs and other animals is at once followed by glycosuria, which soon becomes very severe. The animals waste rapidly, the urine contains β -oxbutyric acid and aceto-acetic acid as well as glucose, and death occurs in four to ten days. During life the urine contains an excess of sugar, and after death the liver is found to be almost free from glycogen. These symptoms are not due to the absence of the pancreatic juice from the digestive tract, since ligation of the pancreatic duct does not lead to glycosuria. Nor do they occur if a small portion, one-eighth or more, of the pancreas is left in the body, although the subsequent removal of this fragment is followed by the train of symptoms just described.

RELATION OF THE PANCREAS TO DIABETES.—It has been proved beyond question that the pancreas furnishes to the blood an internal secretion, which is essential for the proper metabolism of carbohydrate. This internal secretion, to which the name *Insulin* has been given, was first satisfactorily isolated from the pancreas by Banting and Best in 1922. Insulin is formed, not in the secreting acini of the pancreas, but in the *islets of Langerhans*, which are seen scattered throughout the organ in most animals (Fig. 160). In certain fishes there occurs a portion of the pancreas, separate from the rest of the organ, and containing only islet tissue; from this tissue a very abundant yield of insulin can be obtained.

The cells of the islets of Langerhans differ in appearance from the secretory cells of the acini of the pancreas, and two kinds of islet cells called the α and the β cells can be observed. The α cells are fixed by alcoholic fixatives, and form about one-third of the total cells of the islets. The β cells, which form the remaining two-thirds, are fixed by aqueous fixatives, and contain granules which stain with neutral gentian violet. These cells

form the insulin, and the granules which are demonstrable in them are regarded as consisting of a precursor of insulin, ready to be put forth into the blood. When the pancreatic duct is ligatured, the pancreatic secreting tissue undergoes atrophy, but the islet tissue persists, and glycosuria does not develop; from such an atrophied pancreas a large yield of insulin can be obtained.

It might be expected that, if the islets produce an internal secretion essential for normal carbohydrate metabolism, the removal of the greater part of the pancreas would lead to over-activity of the islets still remaining. That this is so has been demonstrated by histological and other methods. When the pancreas is almost completely removed, only a small fragment being left intact, the animal remains well for a time, but eventually develops diabetes of a mild character. Subsequent examination of the small pieces of pancreas left in the animal shows that the tissue of the islets has lost its granules, and has undergone other histological changes. It has yet to be proved, however, that these changes are the cause and not a result of the diabetes.

FAT METABOLISM IN DIABETES.—The failure of the tissues to utilise carbohydrate also affects the metabolism of both fat and protein. In the first place, the oxidation of fat is incomplete, and β -oxybutyric and aceto-acetic acids appear in the blood and combine with some of the sodium bicarbonate with a corresponding liberation of CO_2 . In consequence the respiratory centre is greatly stimulated (this is *air-hunger*). The urine, which is much increased in amount (polyuria), contains the β -oxybutyric acid and aceto-acetic acid, both of which can be readily identified. The latter acid also decomposes with the production of acetone, which can be smelt in the breath and the urine.

PROTEIN METABOLISM IN DIABETES.—Since carbohydrate is not available, the tissues are compelled to rely solely on fat and protein as sources of energy for the production of heat and the performance of work; as a result the excretion of the end-products of protein metabolism in the urine is increased. Indeed, it is probable that, although glycosuria is the most obvious symptom of experimental diabetes, this condition also involves serious disturbance of many other metabolic processes in the body.

DIABETES IN MAN.—This is characterised by hyperglycæmia and glycosuria and is due to a failure of the islets of Langerhans to produce the requisite quantity of internal secretion (insulin); the tissues are therefore unable to burn sugar; this is shown by the fact that, in severe cases, the respiratory quotient is low (0.7) even when the diet contains abundance of carbohydrate. The blood contains an excess of glucose, and at first

this is derived only from carbohydrate. Glucose appears in the urine after administration of amounts of glucose (*e.g.* 100 grammes or less) readily borne by normal persons. Moreover, after a glucose test-meal, the blood-sugar curve (p. 404) reaches a higher level (over 0·2 per cent.) and remains high for a longer period than in normal subjects. Eventually glucose is also formed from protein, and, even on a diet almost free from carbohydrate, large amounts of glucose may be excreted in the urine. Further, it is found that the nitrogen of the urine bears to the glucose (the G : N ratio) a constant relationship. This clearly indicates that protein is the source of glucose on which the body is drawing. In the later stages of the disease, the urine also contains β -oxybutyric acid and aceto-acetic acid, often in large amount.

Many patients finally pass into a state of coma, associated with slow, deep breathing (air-hunger), and die in a few hours. In consequence of the deep breathing, the CO_2 content of the alveolar air falls below 2 per cent. in coma. These symptoms were formerly attributed to an *acid intoxication* caused by the accumulation of β -oxybutyric acid in the blood, but as the reaction of the blood may be absolutely normal, the symptoms cannot be due to acid intoxication. There is some evidence that coma may be the result of a direct poisonous action of the salts of aceto-acetic acid on the nervous system. After death the liver is almost free from glycogen, and the pancreas, when properly examined, shows signs of disease in the islets of Langerhans, in which the number of β -cells is diminished. Recent work clearly indicates that diabetes depends upon the deficiency or absence of the internal secretion from the islets of Langerhans.

INSULIN.—Insulin may be prepared from fresh ox pancreas. The tissue is minced with solid picric acid and transferred to acetone, which extracts the insulin in the form of a picrate. The picrate is separated by evaporation, treated with alcohol containing HCl, and again precipitated with acetone. The white precipitate thus obtained consists of insulin hydrochloride.

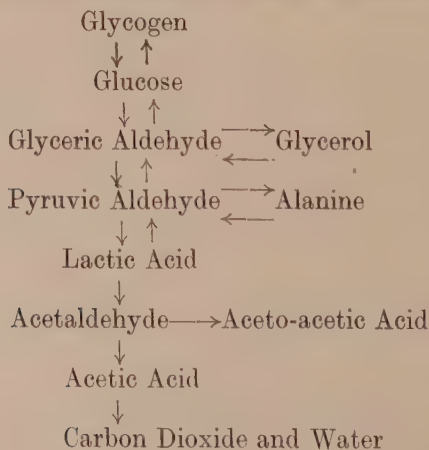
The chemical nature of insulin is unknown, but its physiological properties are very definite. When injected subcutaneously into a normal animal, it causes a rapid fall in the blood sugar, which is most definite if the animal be in the fasting state. When the blood sugar has fallen to about 0·03 to 0·04 per cent., violent *hypoglycaemic convulsions*, due to the abnormally low blood-sugar level, ensue, and the animal may die; the convulsions can be at once cured, and death averted with certainty if an intravenous injection of glucose is promptly given, or even if sugar is given by the mouth. It is not known what happens to the sugar which disappears so speedily from the blood when insulin is given; no

doubt some of it is burnt, though it does not all seem to be accounted for in this way. It is not stored in the liver, because it is found that all the glycogen has vanished from that organ, as though in an attempt to prevent the abnormal fall of blood sugar.

When given in appropriate doses to human diabetics, together with a suitable amount of carbohydrate, there is at once a return of the power to utilise the carbohydrate, disappearance of acetone bodies from the breath and urine, and of glucose from the urine. But the dose, always accompanied by suitable quantities of carbohydrate, must be repeated daily. If the carbohydrate is omitted, there is danger of hypoglycæmic convulsions; if these occur, they can be stopped by the administration of glucose.

SECTION V

TOTAL METABOLISM.—The separate consideration of the changes undergone by fat, protein, and carbohydrate, though convenient, represents very imperfectly the complex nature of the metabolic changes, as a whole, in the body. Not only does the presence or absence of each foodstuff modify the character of the metabolism of the other foodstuffs, but, within certain limits, one kind of foodstuff can be transmuted into another. In other words, many of the chemical changes occurring in the tissues and constituting metabolism are reversible. For example, glucose can be formed from some amino-acids, and, conversely, amino-acids may be produced from ammonia and carbohydrate derivatives. The possible course taken in the body by many of these reactions is indicated in the following scheme (modified from Bayliss), in which double arrows represent a reversible reaction:—



Nevertheless, the metabolism of the amino-acids differs from that of fat and carbohydrate in some important respects. (1) Both fat and carbohydrate can be stored in the body as a reserve, whereas protein can only be stored by causing it to assist in the development of additional muscle substance. (2) Fat and carbohydrate are used mainly as a source of energy, and for this purpose they can be almost entirely replaced by protein. (3) But fat and carbohydrate can only replace protein to a limited extent, since some of the amino-acids required for the building up of protein cannot be formed in the body. It is clear, from these considerations, that the general character of metabolism must be greatly influenced both by the nature of the food and by the absence of one or more of the foodstuffs from the diet.

STARVATION. — Metabolism during starvation has been studied in professional fasting men, and also in the lower animals. When food is withheld, the store of glycogen in the body is rapidly used up, and after two or three days the animal derives its energy solely from fat and protein. Metabolism as a whole is diminished, and the consumption of protein is reduced as far as possible, most of the energy needed by the body being obtained by the oxidation of the fat previously present in the fat-depôts. After three or four days the output of nitrogen in the urine reaches a low level, which is maintained until the body-fat has been used up and the sole available source of energy is the tissue-protein. When this stage is reached, the output of nitrogen in the urine shows a rise. From now onward it is found that there is a constant relationship between the CO_2 produced and the nitrogen excreted, *i.e.* both are issuing from a common source, *viz.* body proteins.

The lost body-weight is partly due to the gradual consumption of the fat previously stored in the depôts, and partly to the wasting of other tissues. The loss falls most heavily on the less vital organs, such as the muscles, whereas the heart and central nervous system lose little or no weight. The breaking down of protein during starvation is probably brought about by a process of *autolysis* or self-digestion in the tissues; the amino-acids formed by the disintegration of the less important tissues are carried in the blood-stream and made use of by the vital organs to make good their daily wear and tear. A similar process of autolysis has been observed in the salmon; during its stay in fresh water the salmon takes little or no food, and the development of the sexual organs, which takes place during this period, is effected at the expense of the skeletal muscles, which undergo autolysis. In man, the character of the metabolism of fat and protein is modified

during starvation, as is shown by the appearance of creatine and of β -oxybutyric acid and aceto-acetic acid in the urine.

In man, the daily excretion of nitrogen in the urine during starvation falls to 9 or 10 grammes or even less, and it might be expected that, if this amount of nitrogen were taken in the form of protein food, it would be used to replace the daily disintegration of tissue in the body, and would not appear in the urine. Experiment shows, however, that such additional protein is almost entirely used to supply energy to the body, and that nearly all the nitrogen taken in the protein meal appears in the urine as well as that which was previously being excreted, so that the disintegration of protein in the tissues is only slightly diminished. When protein is the sole article of diet, it is necessary, in fact, to give by the mouth a quantity of protein containing three or five times as much nitrogen as that which was previously being excreted during starvation in order to obtain a balance between the intake and output of nitrogen. The balance is called *nitrogenous equilibrium*. A further increase in the amount of protein taken by the mouth does not lead to a retention of nitrogen in the body, but the amount of nitrogen excreted increases until nitrogenous equilibrium is again reached at a higher level than before.

Day.	Intake of Protein.	Output of Nitrogen to Urine in Terms of Protein.
1	80 grammes	80 grammes
2	238 "	194 "
4	238 "	220 "
6	238 "	228 "
8	238 "	238 "

In the experiment recorded in the foregoing table the animal on the first day was in nitrogenous equilibrium. When it received three times as much protein, it again reached nitrogenous equilibrium in the course of the next seven days.

If the food does not consist solely of protein, but also contains fat and carbohydrate, most of the energy of the body is derived from the latter, and nitrogenous equilibrium can be maintained on a comparatively small amount of protein; the protein is then used mainly to repair tissue-waste.

THE SOURCES OF MUSCULAR ENERGY.—The muscles form about 40 per cent. of the weight of the body, and their metabolic activity furnishes the greater part of the energy set free as heat

or work in the body. This energy can be derived from all the foodstuffs, and the relative amounts of the different foodstuffs used by the muscles during muscular exercise may be ascertained by observing (1) the total excretion of nitrogen in the urine, and (2) the respiratory quotient.

When protein is the principal or sole food, the amino-acids serve as a source of muscular energy, and the output of nitrogen in the urine (which serves as an index of protein katabolism) is increased by muscular exercise. This has been clearly shown in dogs which were made to do work when fed entirely on lean meat; their bodies contained hardly any fat or carbohydrate, so that amino-acids must have been the chief source of muscular energy. If, however, the diet contains an adequate supply of fat and carbohydrate, the excretion of nitrogen in the urine is not appreciably increased by muscular work, and the energy must be supplied by the oxidation of fat and carbohydrate.

The respiratory quotient varies with the nature of the foodstuffs which are undergoing oxidation in the tissues; and the fact that the respiratory quotient rises slightly during muscular work, whether the diet is rich or poor in carbohydrate, indicates that the active muscle obtains a rather larger proportion of its energy from carbohydrate than does the resting muscle.

Nature of Diet.	Respiratory Quotient in Man.	
	Rest.	Work.
(1) Rich in carbohydrate .	0·85	0·92
(2) Poor in carbohydrate .	0·79	0·82

But, although the active muscles appear to display some preference for carbohydrate as a source of energy, there is every reason to believe that the energy expended during muscular work is normally derived from the oxidation not only of carbohydrate but also of fat.

CHAPTER XVII

ENERGY METABOLISM

SECTION I

METHODS OF INVESTIGATION.—Every movement of the body, every heart-beat, every secretory act demands the expenditure of energy. The normal source of this energy is the food-stuffs.

Our knowledge of the energy exchange is still very imperfect. But their main outcome is the conversion of the potential energy of the foodstuffs into kinetic energy, which is utilised either for the performance of external muscular work or for the maintenance of the body temperature. During this process fats and carbohydrates are completely oxidised to carbon dioxide and water, whereas the proteins are converted partly into carbon dioxide and water, and partly into urea and other incompletely oxidised nitrogenous substances, which are excreted in the urine. Nearly all the carbon dioxide is removed from the body through the lungs, and the water by the respiratory tract, kidneys, and skin. Further, in carrying out these oxidative changes, the tissues must use oxygen. The amount of oxygen taken up by the body in a given time furnishes a rough index of its metabolic activity.

The metabolic (chemical) activities of the body may therefore be studied in four ways: (1) by measuring the heat evolved by oxidation of the food; (2) by measuring the energy expended by the body as work and heat in a given time; (3) by determining the amount of oxygen required for the oxidative processes which provide this energy; and (4) by measuring the amount of CO_2 and other end-products which are formed. Although these methods measure the total metabolic activity of the body, they throw but little light on the nature of the processes involved; and for this purpose they must be supplemented by a study of the material metabolism, that is, the actual changes undergone by the individual foodstuffs within the tissues themselves. This has been done in Chapter XVI.

FOOD CALORIMETRY.—The heat evolved by the complete oxidation of a foodstuff can be ascertained by means of the bomb-calorimeter (Fig. 168), which consists of a metal bomb, A, through the top of which pass two wires, *h* and *h'*, connected below by a strip of soft iron wire, B; one gramme of the substance, *e.g.* glucose, which is to undergo combustion is placed in contact with the iron wire. The bomb is filled with oxygen from a cylinder under a pressure of 7 to 8 atmospheres, and is enclosed in a bath, C, containing a known volume of water, and surrounded by an air-jacket, E, and a water-jacket, D. When a current is passed through the wires, the soft iron fuses and ignites the sugar, which is rapidly oxidised to carbon dioxide and

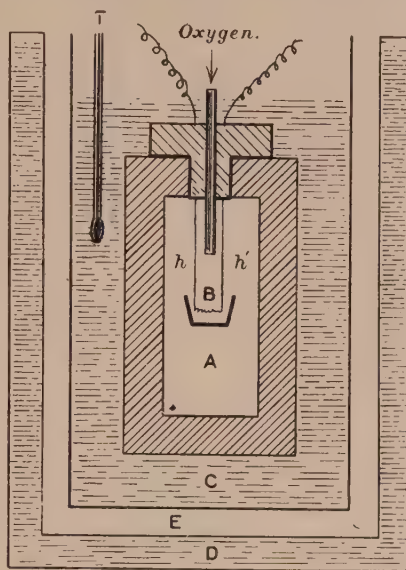


FIG. 168.—Bomb-calorimeter.

T, thermometer; E, air-jacket; B, strip of iron wire.

water. The heat evolved in this process raises the temperature of the water in which the bomb is placed; and, if the temperature of the water before and after combustion be observed, the amount of heat evolved can be calculated, and is expressed in *calories*. A (large) Calorie is the amount of heat required to raise 1000 grammes of water 1°C . If the volume of water in such an experiment is 1 litre and the rise of temperature is 4.1°C , 1 gramme of sugar when fully oxidised gives out 4.1 calories; this amount, which is spoken of as the calorie-value of glucose, is constant. The average calorie-values of fat, carbohydrate, and protein are shown in the following table:—

Protein, 1 gramme	= 4.1 Calories.
Fat, 1 gramme	= 9.3 „
Carbohydrate, 1 gramme	= 4.1 „

The calorie-value of protein when completely oxidised in the calorimeter is 5.6; but protein is not fully oxidised in the body, its nitrogen being excreted in the urine largely as urea, and to a less extent as other substances, each of which has a calorie-value of its own. In determining the physiological calorie-value of

protein, the heat-value of urea and other nitrogenous products must be deducted from the figure 5·6. The calorie-value of protein in the body is thus reduced to 4·1.

BODY CALORIMETRY.—The energy set free in the body by the oxidation of foodstuffs appears partly as heat and partly as muscular work. The energy set free as muscular work may be calculated as heat according to the following equation :—

$$425 \text{ kilogram-metres of work} = 1 \text{ large Calorie.}$$

The heat formed in the body can be determined by placing a man in a suitable calorimeter. This method is known as *direct calorimetry*. Large calorimeters such as that of Atwater and Benedict have been constructed in which a man can live and carry out muscular work for two or three days or longer. (See Fig. 169.) The calorimeter consists of a room with double,

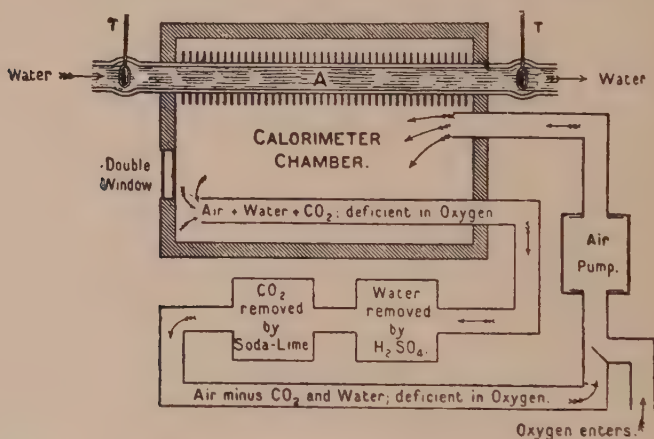


FIG. 169.—Diagram to show the principle of the Atwater-Benedict calorimeter. (After Halliburton.) (From Starling's *Principles of Physiology*.)

non-conducting walls. Embedded in these are a series of pipes through which cooled water is flowing at such a rate that the temperature of the room remains constant. The heat given off by the man warms the water passing through the pipes, and is thus carried off. By measuring the amount of water flowing along the pipes and the rise in its temperature as it passes through the calorimeter, the total heat lost by the individual can be estimated; and, since his temperature remains steady, this is equivalent to the heat produced by him in a given time.

THE CONSERVATION OF ENERGY.—By means of this method it is possible to determine (1) the energy supplied to the body in the food, and (2) the energy lost from the body as heat and muscular work. These two balance one another within the limits of experimental error, and the energy lost has its origin entirely in the potential energy supplied in the food. The principle of the conservation of energy is as true for living beings as it is in the inorganic world.

Consider, for example, the following table by Atwater (average of a four days' experiment) :—

A = Heat of combustion of food eaten	2519
B = Heat of combustion of urine and fæces	245
C = Heat of combustion of protein and fat lost by the man	83
D = A + C - B (energy of food available)	2357
E = Energy measured by calorimeter	2397
F = Difference per cent. between D and E	1.7

It will be seen that D and E are very close indeed to one another. In this experiment the calorimeter registers a little more heat than the man's food provides for. In another experiment it may record a little less. On the whole, agreement is extraordinarily close.

INDIRECT CALORIMETRY.—Since practically all the carbon of carbohydrate and fat and nearly all that of protein is oxidised to CO_2 , by measuring the latter we can estimate the former. But, unfortunately, the heat evolved when the different foodstuffs are oxidised differs, and therefore in addition to knowing how much oxygen has been used, or CO_2 given out, we must also know what proportion of each food has been oxidised. Luckily, protein can be neglected from the calculation and the ratio of protein to fat can be ascertained from the respiratory quotient.

The respiratory quotient and exchange, during short periods, are determined by Douglas's method (Fig. 170). By means of a mouthpiece provided with appropriate valves, the air expired during a known period of several minutes' duration is collected in a large rubber-lined bag. This expired air is well mixed, a sample is analysed, and its total volume is found by expressing it from the bag and passing it through a gas-meter. From the total volume of the expired air, and from the excess of carbon dioxide and deficit of oxygen in it, as compared with inspired air, the respiratory exchange and quotient may easily be calculated, as explained on p. 172.

Thus, if during five minutes the volume of air collected was 30 litres and the volume per minute was 6 litres; if it

contained 4.06 per cent. more CO_2 than the inspired air, then the volume of CO_2 expired per minute would be 243.6 c.c. (i.e. $4.06 \times 10 \times 6$); if by a similar calculation to the one given on

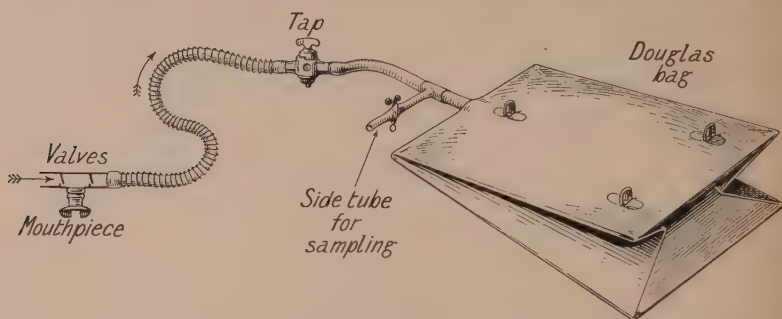


FIG. 170.—Diagram of Douglas bag arranged for collection of the expired air.

p. 172, the oxygen deficit of the expired air was found to be 4.57 c.c. per cent., then the oxygen usage of the body per minute would be $4.57 \times 10 \times 6 = 274.2$, and the R.Q. $\frac{243.6}{274.2} = 0.89$.

Now the number of c.c. of oxygen absorbed in order that 1 calorie shall be produced by oxidising some of the food is given by the formula $198.1 + 51(1 - \text{R.Q.})$. Then in the case we are considering, the number of c.c. per calorie is $198.1 + 51(1 - 0.89) = 203.7$, and the number of calories evolved per minute is $\frac{274.2}{203.7} = 1.346$, which would be 1940 calories per day.

FOR SMALL ANIMALS the apparatus devised by Haldane and Pembrey, and shown in Fig. 171, may be employed. The animal, e.g. a mouse, is placed in a vessel C, through which is

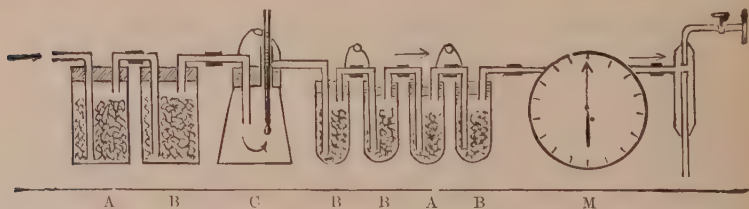


FIG. 171.—Haldane-Pembrey respiration apparatus for mouse.
(From *Practical Physiology*, by Pembrey and others.)

A, soda-lime; B, H_2SO_4 ; C, chamber for animal; M, gas-meter.

drawn a current of air, freed from carbon dioxide and water by passing it through soda-lime and sulphuric acid. The water in

the air leaving the chamber is absorbed by pumice saturated with sulphuric acid in the tubes B B ; these are weighed before and after the experiment, the increase in weight representing the water given off by the animal. The carbon dioxide evolved is absorbed in the tubes A, which contain soda-lime, and the water taken up from the soda-lime is absorbed by sulphuric acid in the tubes B ; these tubes are weighed before and after the experiment. The animal loses weight because the weight of carbon dioxide and water given off exceeds the weight of oxygen taken into its tissues. The amount of oxygen taken up by the animal can be determined indirectly by subtracting the loss in weight of the animal during the experiment from the total weight of carbon dioxide and water given off. To calculate the respiratory quotient and exchange, the weights of oxygen and carbon dioxide are converted into volumes.

SECTION II

THE EFFECT OF EXERCISE.—During muscular activity the chemical changes in the muscles are increased ; heat is evolved, more oxygen is used, and, as the muscles form about 40 per cent. of the total weight of the body, the respiratory exchange during muscular exercise may be from eight to ten times greater than during rest.

RESPIRATORY EXCHANGE IN MAN. (Benedict and Cathcart.)

	Oxygen absorbed in c.c. per Minute.	Carbon Dioxide discharged in c.c. per Minute.
Resting . . .	242	218
Moderate work . . .	1490	1224
Severe work . . .	1850	1789

THE EFFECT OF BODY SURFACE.—The respiratory exchange varies with the size of the animal. The smaller the animal the greater is its surface relatively to its weight, and, since the body loses heat chiefly from its surface, the relative loss of heat must be greater in a small than in a large animal. In order to make up for this loss the smaller animal must produce a relatively larger amount of heat, and must use up in this process relatively more oxygen, than a bigger animal. It is found, in fact, that metabolism is more active and the respiratory exchange greater, weight for weight, in small animals than in large ones.

The following table shows the relationship between heat production, weight, and surface-area in various animals :—

	Weight in Kg.	Calories produced per Diem	
		Per Kg. of Weight.	Per Square Metre of Surface.
Horse	441.0	11.3	948
Pig	128.0	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Mouse	0.01	654.0	1188

THE ESTIMATION OF BODY SURFACE.—Direct determination of body surface is a laborious procedure. In order to estimate the body surface in man, the weight and height of the subject are determined, and the body surface is then found by reference to a chart constructed by Du Bois on the basis of direct measurements on normal adult subjects (Fig. 172). Thus,

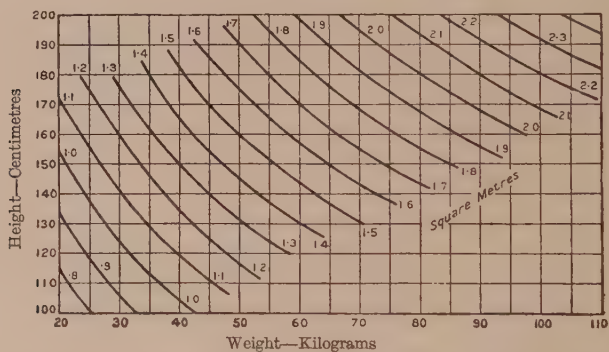


FIG. 172.—Graph for finding the body surface from the weight and height. The curved line, which crosses the point of intersection of the height and weight co-ordinates, gives the body surface, e.g. 60 kg. and 170 cm. give a surface of 1.7 sq. metres. (From Cathcart, Paton & Pembrey's *Practical Physiology*, Edward Arnold & Co.)

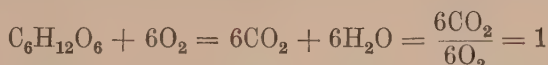
an individual weighing 65 kg. and having a height of 150 cm., has a body surface of 1.6 sq. metres.

The basal metabolic rate per square metre of body surface is in man about 40 calories per hour in the fasting condition; deviations of 15 per cent. on either side of this figure are within the normal range.

Apart from the question of size, the consumption of oxygen is relatively greater in growing than in adult animals, since

oxygen is used not only in the chemical changes necessary to maintain the weight of the animal, but also in the metabolic processes associated with growth.

THE RESPIRATORY QUOTIENT.—The value of the respiratory quotient is determined almost entirely by the nature of the foodstuffs which are being oxidised in the tissues, and this normally depends upon the character of the food consumed by an animal. If an animal were living solely upon carbohydrate food, all the oxygen taken into the body would reappear as carbon dioxide, and the quotient would be 1, in accordance with the following equation :—



If the diet consisted entirely of fat, the oxygen taken into the body would not all reappear as carbon dioxide ; some of it would be used in converting hydrogen into water, and the quotient would be less than 1, the oxidation being represented thus :—



On a purely protein diet part of the oxygen would be combined with nitrogen and sulphur, as well as with hydrogen, and the respiratory quotient would be approximately 0.8. In man living on a mixed diet the quotient is usually about 0.85 ; it is lowered by the exclusion of carbohydrate from the diet, and is raised when the diet consists mainly or exclusively of carbohydrate food. The respiratory quotient is thus of great value, in that it gives an indication of the nature and relative amount of the foodstuffs which are being oxidised in the body under various conditions.

END-PRODUCTS OF METABOLISM.—The whole of the carbon in fat and carbohydrate, and a large proportion of that in protein, is removed from the body in a completely oxidised form as carbon dioxide, while the nitrogen of protein leaves the body in the form of urea, uric acid, and other substances, excreted in the urine. Since protein contains about 16 per cent. of nitrogen, it is possible, by determining the total amount of nitrogen in the urine, to calculate the amount of protein from which it has been derived ; each gramme of nitrogen in the urine represents the breaking down in the body of 6.25 grammes of protein. By measuring the output of nitrogen in the urine and

the amount of carbon dioxide discharged from the lungs daily, the total amount of protein, fat, and carbohydrate which has been oxidised in the body can be calculated, if the respiratory quotient be known. In health the amount of carbon and nitrogen thus removed from the body is equivalent to the amount taken in with the food, provided that the weight of the individual remains steady. If the individual is putting on weight, some of the carbon taken in the food is retained in the body as fat or carbohydrate, and there may possibly be some retention of nitrogen; when weight is being lost, more carbon, and possibly more nitrogen, is discharged than is taken in with the food.

CHAPTER XVIII

FOOD AND DIET

SECTION I

THE substances used as food by man and animals contain protein, fat, carbohydrate, salts, water, and small amounts of essential substances, known as accessory food factors; and in order to construct a suitable diet for man, it is necessary to know, first, what amount of these substances in the food best meets the needs of the body, and, second, the composition of the different foodstuffs.

The mere composition of the foodstuffs, however, is an uncertain guide to their true nutritive value, since this depends upon the ease with which they can be digested and assimilated; it is important, therefore, that the food should be palatable, digestible, and readily absorbed.

DIET.—The body may be regarded as a machine which converts the potential energy of food into the kinetic energy of muscular work and heat. The living tissues also undergo a constant wear and tear, the tissue which is broken down being replaced by fresh tissue built up from the absorbed foodstuffs. In growing animals, too, there is a conversion of absorbed digestion products into new tissues. In addition certain essential substances, the vitamins, are required for the protection of the body against disease. A suitable diet, therefore, fulfils three functions: (1) it serves as a source of energy; (2) it contains the constituents necessary to replace lost or to create new tissue; and (3) it contains the protective vitamins.

DIET AS A SOURCE OF ENERGY.—If the muscular work performed be calculated in terms of heat, it is found that the daily output of energy in man in the form of heat and work is usually about 3000 large Calories (Fig. 173). It is less in those who lead a sedentary life, and is reduced to a minimum during complete rest in bed. Even then, however, energy is being used in maintaining the temperature of the body and in the

carrying out of respiration, digestion, and other internal bodily functions. The energy expended in carrying out these processes, which are essential for the continuance of life, constitutes the "basal metabolism" of the body; it is approximately 1 Calorie per 1 kg. of body-weight per 1 hour, and amounts to 1700 to 2000 Calories a day. Hard physical work may increase the daily expenditure to 4000 to 5000 Calories or even more.

It is clear that the amount of potential energy which must be supplied in the food must at least be equal to the sum of the indispensable minimum compatible with life (the basal metabolism)

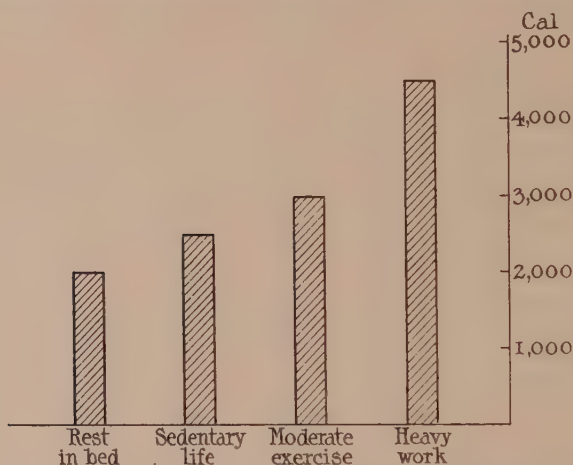


FIG. 173.—Chart showing the average daily expenditure of energy (in calories) under various conditions.

and the amount put out as work. If the supply of energy in the food is insufficient, a man can perform muscular work only at the expense of the fat and carbohydrate, or even the protein, stored in his body. Another factor which influences the daily consumption of energy, and hence the food requirements of the individual, is the external temperature. Generally speaking, the consumption of heat from the surface of the body is greater in winter than in summer, and, since external cold stimulates metabolism, there is a corresponding increase in the amount of food required. Mental work has comparatively little influence on the daily expenditure of energy by the body.

As we have seen (p. 415), the average physiological calorie-values of the foodstuffs are as follows :—

1 gramme protein	= 4.1 Calories
1 „ fat	= 9.3 „
1 „ carbohydrate	= 4.1 „

From these data it is easy to draw up a diet containing the food-stuffs in such amount that, when oxidised in the body, they will furnish sufficient energy to replace the daily expenditue. Experience has shown that the following represents the proportions of the different foodstuffs most suitable for a man doing a moderate amount of muscular work :—

Protein	100 grammes	$\times 4.1 =$	410 Calories
Fat	100	„ $\times 9.3 =$	930 „
Carbohydrate	500	„ $\times 4.1 =$	2050 „
			3390 Calories

At least 5 per cent. must be deducted from the calorie-value of this diet, since part of the food eaten is not absorbed from the digestive tract, but is lost in the fæces. The same calorie-value could be obtained by combinations of these foodstuffs in other proportions ; and, particularly as regards fat and carbohydrate, the relative amounts of the foodstuffs in the diet are greatly influenced by the readiness with which they can be obtained, by their cost, and by the tastes of the individual.

THE REPLACEMENT OF WEAR AND TEAR.—In order to replace the breaking down of the tissue-proteins, the diet must contain a certain minimum of protein, and there has been much discussion on the amount of protein most suitable for the needs of the body. Chittenden considers that the amount of protein consumed by most people is excessive, that it can be largely replaced by fat and carbohydrate as a source of energy, and that a comparatively small amount of protein is needed to repair tissue-waste and to maintain nitrogenous equilibrium. Any excess of protein beyond this minimum he regards merely as throwing additional work on the liver and kidneys in excreting its nitrogen. He found by observation on himself and others that it was possible to maintain health and nitrogenous equilibrium for six to eighteen months, and to carry out muscular work, on a diet containing much less protein than that in the dietary mentioned above ; in many cases the daily intake of protein did not exceed 40 to 60 grammes.

His views have not met with general acceptance. (1) Individuals living on such a low protein diet are apt to suffer in general health and in their ability to resist infection. (2) The diet of an infant contains much more protein than the minimum which would be necessary according to Chittenden's views, and, since Nature provides more than the minimum of protein, the minimum is probably not the optimum. (3) In view of what has been

already said (p. 398) as to the amino-acids which are essential for growth and maintenance, it is obvious that different proteins will vary in their nutritive value, sometimes called their "biological" value, according to the nature and proportions of the various amino-acids contained in them. Some, as for example gelatin, will be used mainly to supply energy, whereas others, containing tyrosine, tryptophane, and cystine, will be of value for the building up of the tissues. Hence, while a diet containing 60 grammes of one protein, say caseinogen, may provide the amount of the essential amino-acids required by the body, a diet containing the same weight of certain other proteins might be totally inadequate. Broadly speaking, we may regard 100 to 110 grammes of mixed proteins as representing the optimum daily intake for most men. The protein requirements of women are rather less, being from 80 to 90 grammes. Violent exercise increases the wear and tear of the muscles, and under conditions of severe physical stress, for example in soldiers during war, considerably larger amounts of protein may be necessary to maintain health.

PROTEIN EXCESS.—Having pointed out the defects of protein insufficiency, it may be well to indicate the disadvantages of protein excess. (1) Protein is not a concentrated diet; even lean beef contains about 70 per cent. of water. (2) Its calorie-value is low. In consequence, large quantities of meat would have to be consumed if any serious attempt were being made to reduce the fat and carbohydrate of the diet to a low value. Two difficulties would probably be met with: indigestion and expense. But, (3) the specific dynamic action of the proteins on the metabolism of the body would probably make the diet very inconvenient except in cold weather.

SECTION II

VITAMINS.—Besides serving as a source of energy and supplying a sufficiency of protein, the diet normally contains minute quantities of certain substances, known as *vitamins*, the presence of which is essential for growth and for the maintenance of health. When young rats are fed on an artificial milk containing perfectly pure caseinogen, fat, and milk-sugar in the same proportions as in milk, together with salts and water, the animals fail to grow (Fig. 174), although their diet is adequate both as a source of energy and as regards the amount of protein present. On the addition to this diet of very small quantities of fresh milk, growth takes place in a normal manner. Evidently

the natural food contains something essential to growth, which is removed in the purification of the constituents of the artificial diet. Further investigation has shown that several accessory substances are concerned, and that, in order to ensure normal growth, these substances must be supplied in the food (Fig. 175).

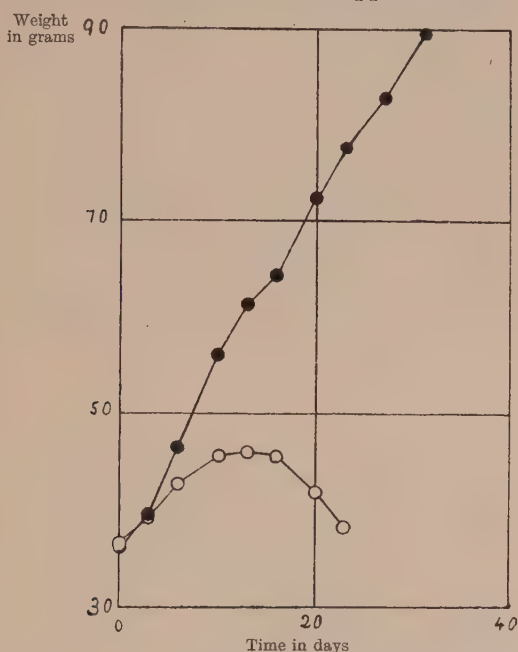


FIG. 174.—Curves showing the effect of nature of diet on growth. (Hopkins.)

Lower curve (white circles)—rats fed on artificial milk alone.
Upper curve (black circles)—rats fed on artificial milk + 2 c.c. of cow's milk daily.

VITAMIN A is a fat-soluble stable chemical substance resisting heating at 200° C. and saponification, but destroyed by oxygen and sunlight. It is present in all animal and fish fats, particularly the liver-fats. Cod-liver oil is the standard example. Milk also contains it. Its absence from the diet causes: xerophthalmia, that is, inflammatory changes of the anterior eye structures; atrophy of the intestinal tract, and keratinisation of the respiratory passages. Additional quantities are required during growth, pregnancy, and lactation.

VITAMIN B probably consists of a mixture of Vitamins F and G. Both are water-soluble substances resisting boiling in acid but not in alkaline media. Both are found in fresh vegetables; in yeast and yeast preparations (Marmite); in meat, eggs, and

VITAMIN C is water-soluble. It is destroyed by boiling in an acid medium in the presence of oxygen. It is found in fresh



FIG. 176.—A. Pigeon suffering from polyneuritis. B. The same bird after treatment with vitamin B. (Funk.) (From the *British Medical Journal*.)

fruit and vegetable juices ; milk contains it, especially in summer. Its absence causes scurvy : (1) bleeding from gums, intestine, kidney, etc. ; (2) tenderness of limbs.

VITAMIN D is fat-soluble like A. Most animal oils contain both. Vitamin D is produced by sunlight from ergosterol. (Sunlight, on the contrary, destroys Vitamin A). Its absence

causes rickets in children and osteomalacia in adults. Rickets : (1) the bones become soft and may bend under the pull of the muscles ; (2) the teeth are defective and decay readily ; (3) respiratory and digestive disturbances ; (4) examination of the calcium and phosphorus of the food and the excreta shows that the body is losing both during rickets. Osteomalacia is a kind of adult rickets affecting pregnant women. The bones soften and become malformed, particularly those of the pelvic girdle. When the pregnancy is completed, the disease still continues until lactation is completed. Then the bones harden again. The administration of Vitamin D (better with calcium) cures the condition.

VITAMIN E is fat-soluble and stable to heat and light. It is found in most vegetable oils. The absence of Vitamin E causes atrophy of the seminiferous tubules in the male and death of the foetus in the pregnant female.

VITAMINS F AND G.—See Vitamin B.

SECTION III

ESSENTIALS OF AN ADEQUATE DIET.—The animal body is unable to manufacture the accessory factors, and animals (including man) can obtain these factors only from their food. It is of the utmost importance, therefore, that the diet should be sufficiently varied in character to provide an adequate supply of all the necessary factors ; and a varied and carefully chosen diet appears to be particularly necessary in childhood, since there is some reason to believe that, as compared with the adult, the growing child requires a relatively large amount of the accessory factors.

We see, therefore, that in order to maintain health the diet must fulfil the following conditions : (1) It must provide sufficient potential energy to replace that lost as work and heat. (2) It must contain enough of the amino-acids necessary to replace the breaking down of the tissues and to provide the complex chemical groupings which the body cannot make for itself. (3) It must contain the accessory factors requisite for maintenance and growth.

Salts and water must also be present in the diet, although they do not supply energy. Further, in young growing animals the diet, especially protein food, must be relatively more abundant than in adults. Not only is metabolism more active in young

animals, but an additional amount of protein is required to provide material for the laying down of new tissue during growth.

THE CONSTRUCTION OF A DIETARY.—The amount of protein, carbohydrate, fat, salts, and water required daily being known, a dietary can be constructed with the aid of a table



FIG. 177.—Composition of staple foods shown diagrammatically.

Red = protein; yellow = fat; shading = carbohydrate; unshaded part = water and salts.

showing the composition of foodstuffs such as that given below. Fig. 177 gives a graphic representation of the composition of certain staple foodstuffs.

Approximate Composition of some Common Food-stuffs.						
	Protein.	Carbo- hydrate.	Fat.	Salts.	Water.	Unavailable.
Lean beef . . .	20.3	...	7.5	1.1	70.0	1.1
Eggs . . .	13.0	...	10.0	0.8	73.7	2.5
Milk (cow's) . . .	3.5	4.5	4.0	0.7	86.8	0.5
Cheese . . .	25.1	2.4	32.0	2.9	34.2	3.4
Peas (dried) . . .	17.3	62.5	0.9	2.2	9.5	7.6
Oatmeal . . .	13.4	65.2	6.6	1.4	7.8	5.6
Rice . . .	6.5	76.9	0.3	0.3	12.3	3.7
Bread . . .	7.1	52.3	1.2	0.8	35.3	3.3
Potatoes . . .	1.7	17.7	0.1	0.8	78.3	1.4
Carrots . . .	0.7	8.9	0.4	0.8	88.2	1.0
Butter . . .	1.0	...	80.8	2.3	11.0	4.9

It will be observed that the animal foods are especially rich in protein and fat, and in ordinary life most of the necessary protein is taken in the form of beef, mutton, and eggs. Vegetable foods, on the other hand, are the chief source of carbohydrates, and the latter substances in a dietary are usually derived from bread, rice, and potatoes. Most vegetable foods contain a considerable amount of protein, but the amino-acids are present in these proteins as a general rule in proportions which are somewhat different from those contained in the body proteins. A man proposing to live on an exclusively vegetable diet should bear this important fact in mind. Whereas 80 grammes meat protein per diem may suffice, 160 grammes vegetable protein may be found necessary for complete nitrogenous equilibrium.

If the amounts of the alimentary principles required daily be taken as :—

Protein	100 grammes
Carbohydrate	450 „
Fat	100 „
Salts	30 „

a dietary may be constructed from the table of foodstuffs as follows :—

	Protein.	Fat.	Carbohydrate.	Salts.
450 grammes bread . . .	32	5.4	233.3	4.5
180 „ meat . . .	37.2	13.5	...	1.8
600 „ milk . . .	21.0	24.0	27.0	4.2
20 „ butter . . .	0.2	20.0	0.2	0.3
300 „ potatoes . . .	5.1	0.3	53.1	2.4
60 „ jam . . .	...	...	36.0	...
50 „ rice . . .	3.2	0.1	38.0	0.1
60 „ sugar . . .	...	...	60.0	...
60 „ bacon . . .	5.7	35.4	...	2.0
	104.4	98.7	447.6	15.3
Calorific-value 3181				

It will be observed that the salt content of the diet is deficient, and would have to be supplemented by means of common salt.

SECTION IV

MILK.—This is a very valuable foodstuff for individuals of all ages. It contains all the alimentary principles of a dietary, combined in the proportions necessary for the early stages of life.

The proportion of the constituents of milk varies somewhat with the species, as will be seen from the following table :—

	Woman.	Ass.	Cow.
Proteins . .	1.5	1.9	3.5
Fats . .	3.5	1.4	4.0
Lactose . .	6.5	6.3	4.5
Salts . .	0.2	0.4	0.7
Water . .	88.3	90.0	87.3

By comparison of these figures, it will be seen that cow's milk contains too large a proportion of protein, and too small a proportion of lactose, for the human infant. It is therefore advisable, if an infant is fed on cow's milk, to dilute the latter with water and to add lactose and a little cream in order to obtain the correct proportions.

Fresh cow's milk has a specific gravity of 1028 to 1034, and is neutral to litmus. Microscopically, it consists of small globules of fat floating in an almost colourless fluid, that is, it is a permanent fine emulsion. The globules appear to be prevented from running together by the proteins of the milk which form a fine pellicle on the surface of each globule.

MILK PROTEINS.—The proteins of milk are caseinogen and lactalbumin. Caseinogen is a phospho-protein, and is insoluble in water, but soluble in dilute alkalies. It exists in milk as a compound with calcium, and is precipitated by the addition of acetic acid, the precipitate being soluble in excess of the acid. The precipitate of caseinogen obtained from milk by the addition of acetic acid carries down the fats entangled with it, and may be purified from these by washing with ether. When purified, it is a white powder. Lactalbumin remains in the filtrate when the caseinogen and fats have been filtered off. If the excess of acid in the filtrate be almost neutralised so that only a trace of acidity remains, the lactalbumin may be coagulated by heating the fluid.

The suitability of the maternal milk for the needs of the growing animal does not depend only on the fact that the various constituents are in the correct proportions. As has already been pointed out, every protein consists of a characteristic grouping of amino-acids, some of these acids being present to a special extent in one protein, and others in another. Caseinogen is remarkable in that nearly all the amino-acids which enter into the composition of the various proteins are represented in its structure to a greater or less extent, so that it may form a source from which any of the body proteins may be built up. The

only necessary amino-acid absent from caseinogen is glycine, and glycine can be synthesised in the body. Caseinogen contains very little cystine, but this defect is remedied in milk by the presence of lactalbumin, which contains a considerable amount of cystine.

When acted on by "rennet" ferment, the caseinogen of human milk is thrown down in the form of a flocculent precipitate, whereas cow's milk forms a firm, massive clot. For this reason cow's milk, even when diluted, does not form for the human infant a satisfactory substitute for maternal milk. Other drawbacks to the "bottle-feeding" of infants are: (1) the difficulty of obtaining sterile cow's milk; (2) the fact that sterilisation can only be effected at the cost of losing a proportion of the accessory factors; and (3) the loss to the child of anti-bodies which are present in the maternal milk and help to protect it from certain infective diseases.

MILK FAT, SUGAR AND SALTS.—The fats of milk consist mainly of tripalmitin, tristearin, and triolein; the complex fat, lecithin, is also present. There are, in addition, small quantities of fatty acids lower in the scale—myristic, caproic, caprylic, and lauric acids.

Lactose is the carbohydrate present in milk. If milk is treated with acetic acid so as to precipitate caseinogen, and is then filtered, the filtrate contains lactose; if the filtrate is allowed to evaporate slowly at a comparatively low temperature, the lactose crystallises out.

The salts of milk consist chiefly of phosphates and chlorides of potassium, sodium, calcium, magnesium, and iron, calcium phosphate being the most abundant. Analyses have shown that these salts are present in the milk of any one species in exactly those proportions in which they occur in the young animal which is nourished on that milk. A large proportion of calcium phosphate is of especial importance in view of the formation of bone in the growing animal.

When milk is allowed to stand it becomes sour. The acidity is due to the formation of lactic acid from the lactose by the agency of certain organisms, such as *bacillus acidi lactis*, which readily make their way into milk. The lactic acid, like acetic acid, precipitates the caseinogen, and the latter entangles the fats, forming a curd. The precipitation of caseinogen in this way must not be confused with the clotting of milk which is brought about by ferment action in the stomach (p. 360). In the latter process the caseinogen undergoes a chemical change, being converted into casein.

FOODSTUFFS DERIVED FROM MILK.—The *cream* of milk contains 41 to 44 per cent. of fats, and is a useful means of administering fat when an extra amount is required in the dietary. *Butter* is obtained by separating the fats from cream, and is almost pure fat with a trace of protein and a small percentage of water. *Cheese* is made by the compression of clotted milk so as to express as much as possible of the water. Cheese is thus rich in protein and fat, the protein being chiefly casein. It contains hardly any sugar.

SECTION V

BREAD.—Flour contains 68 per cent. of starch, 12 per cent. of proteins, and small quantities of cellulose, fats, and salts. When it is kneaded with water, a change takes place in its proteins. These are two in number, namely *gliadin*, which is soluble in alcohol, and *glutenin*, which is insoluble in alcohol. When flour is mixed with water these two substances are converted into the sticky material *gluten*. Dough is thus formed mainly of gluten and starch. It is made spongy by the liberation of gases in its interior, usually by the action of yeast. In the process of baking, the starch in that portion of the loaf which is most exposed to the high temperature—namely, the crust—is partially converted into dextrin and caramel.

MEAT FOODS.—The composition of lean beef is given in the table on p. 431. Fat beef contains nearly as much protein, more fat, and less water. Mutton, poultry, and white fish contain about the same proportions of the various constituents, but poultry contains rather more protein and a smaller proportion of salts than beef, whereas white fish contains less protein and more water.

EGGS.—The white of egg contains three proteins, egg-albumin, egg-globulin, and ovomucoid. The yolk contains a small amount of vitellin (a phospho-protein) and a large proportion of fats, with smaller quantities of cholesterol, lecithin, sugar, and salts.

GREEN VEGETABLES.—Green vegetables are of little value as a source of proteins, carbohydrates, and fats. They have, however, three important functions in a dietary : (1) as a source of iron, (2) as a source of vitamins (p. 427), and (3) as mechanical stimulants to the peristaltic movements of the digestive tract, in virtue of the indigestible cellulose which they contain.

ROOT AND SEED VEGETABLES.—These are very valuable foods indeed, because (a) their cost is low, (b) they are very readily transported, (c) they can usually be kept for long periods without deterioration, (d) they contain high percentages of the essential foodstuffs. For example, dried peas have a protein content of 17·3 per cent. and a carbohydrate content of 62·5. For oatmeal the figures are 13·4 per cent. and 65·2 per cent. respectively. In addition there is 6·6 per cent. of fat. Soya flour, which will soon be available in large quantities, is particularly rich in proteins and fats.

GELATIN.—This is a sclero-protein, and is formed by boiling collagen, the principal solid constituent of connective tissue. Gelatin cannot entirely replace other proteins in a dietary because it is deficient in three essential amino-acid groups, phenylalanine, tyrosine, and tryptophane; moreover, cystine, the sulphur-containing amino-acid, is absent from the gelatin molecule. In one experiment on a dog, it was found that nitrogenous equilibrium could be maintained when five-sixths of the protein of the diet was replaced by gelatin. In other experiments on animals, it has been found possible to maintain nitrogenous equilibrium for a time on a diet of gelatin to which tyrosine and tryptophane were added.

BEVERAGES.—*Tea* and *coffee* owe their fragrance to aromatic substances, and their stimulating properties to the presence of caffeine (trimethylxanthine). *Cocoa* contains about 30 per cent. of fat and 20 per cent. of protein, and is therefore a food. It has also stimulating properties owing to the presence of theobromine (dimethylxanthine).

Alcohol undergoes oxidation in the body to a limited extent, and to that extent it acts as a food. Its value as a food is, however, more than counterbalanced by its action as a poison. If taken in any quantity, it interferes first with the inhibitory powers of the higher centres of the brain; later it disturbs the mechanism for muscular co-ordination; and finally it paralyses the whole nervous system. The continued use of alcohol, moreover, leads to degenerative changes in the tissues and organs of the body, and in that way it shortens life.

CHAPTER XIX

WARMTH AND VENTILATION

SECTION I

FROM the point of view of their temperature, animals fall into two groups, namely, (1) *poikilothermic*, or cold-blooded animals, whose temperature varies with that of their surroundings, and (2) *homoiothermic*, or warm-blooded animals, whose temperature remains constant except for slight daily variations, and is independent of that of their surroundings. To the former group belong fishes and amphibia, to the latter birds and mammals, including man.

POIKILOTHERMIC ANIMALS.—In cold-blooded animals metabolic activity, including the production of heat, varies with the external temperature, resembling in this respect chemical reactions in the laboratory, which are accelerated by a rise of temperature. Hence the amount of oxygen consumed and of carbon dioxide given off by a poikilothermic animal varies directly with the temperature of its surroundings. These animals possess no regulative nervous mechanism by which they can counteract the effects of heat or cold. When the surrounding temperature falls, their metabolic activities diminish until they sink into a state of torpor. When the temperature rises, their metabolic activities increase, and their only means of evading the ill effects of an unduly high temperature is to hide in a stream or to burrow into moist earth.

HOMOIOTHERMIC ANIMALS.—In these animals the external temperature modifies but little the internal temperature of the animal. Thus man's summer temperature is practically identical with his winter one.

In man the normal temperature is 37°C . (98.4°F .); it shows a daily variation of approximately 1°F ., being highest in the afternoon and lowest in the early morning. It is lowered by starvation or prolonged lack of sleep, and is raised by muscular exercise.

The constancy of the temperature is due to the fact that production and loss of heat balance each other.

PRODUCTION OF HEAT.—The chemical changes in the body which constitute metabolism involve the production of heat, and this takes place chiefly in the muscles, and to a smaller extent in the liver and other glandular organs; the blood leaving the liver, for instance, is warmer than that entering it. The production of heat in the glandular organs is greatest during the periods of their activity associated with the digestion of food, and is comparatively constant from day to day. The heat formed in the muscles, however, varies greatly, being enormously increased by muscular exercise; and in warm-blooded animals the amount of heat formed in the body depends largely upon the degree of activity of the skeletal muscles. As has been pointed out (p. 36), the greater part, three-fourths or more, of the total energy set free during muscular contraction appears as heat. The heat formed in the body can be measured by means of a calorimeter, the most suitable form for man being the Atwater-Benedict calorimeter (p. 416).

LOSS OF HEAT.—Heat is lost from the body principally through the skin, and to a smaller extent in warming the expired air and the excreta. On the average, 77 to 80 per cent. of the heat-loss takes place through the skin, 17 to 20 per cent. is lost from the respiratory tract, and 3 per cent. in the excreta. The total daily loss varies greatly with the conditions under which the individual is living, being as a rule from 2500 to 3500 calories.

THE SKIN consists of two layers: a superficial layer, the epidermis, made up of stratified squamous epithelium, and a deeper layer, the dermis, formed of fibrous tissue. The dermis rests upon connective tissue of a looser texture, which is called the subcutaneous tissue and contains a variable amount of fat.

The *epidermis* has two principal layers: a deeper layer of cells called the *rete mucosum*, and a superficial layer known as the *stratum corneum* or horny layer. The cells of the *rete mucosum* are mostly irregular in shape and are connected by protoplasmic bridges; between these are tiny channels along which lymph for the nourishment of the cells flows.

In the horny layer a transformation has occurred whereby the protoplasm has been converted into *keratin*; at the same time the cells have become flattened and scaly and possess no visible nuclei. Between the *rete mucosum* and the horny layer can be seen two narrow layers, the *stratum granulosum* and the

stratum lucidum, in which cells are undergoing transformation. The surface cells of the epidermis are continually being shed, and are replaced by the multiplication and subsequent alteration of the cells of the rete mucosum.

The *dermis* consists of dense fibrous tissue which presents papillæ or projections on its surface. The epidermis is moulded on these papillæ, and, where they are arranged in rows, as on the palmar surface of the hand and fingers, the epidermis shows corresponding ridges. Blood-vessels run in the dermis and form capillary loops in the papillæ. Lying near the junction of the dermis and subcutaneous tissue over the whole surface of the body are the *sweat-glands*, consisting of coiled tubes, the ducts of which run in a spiral manner through the dermis and open into corkscrew-shaped channels in the epidermis leading to the surface.

THE SEBUM.—The skin is protected and kept supple by sebum, which is a fatty material secreted by the *sebaceous* glands. These glands are found whenever hairs are present, and their ducts open into the upper part of the hair-follicles. Each gland is composed of a solid mass of cells, in the central part of which the cells are loaded with fat and the protoplasm has largely disappeared. The fatty material or sebum is not a true fat, but consists chiefly of fatty acids combined with cholesterol.

The secretion of sebum is always taking place, the semi-liquid central part of the gland being squeezed on to the surface of the skin, whenever the hairs are erected, by the contraction of the arrector pili muscles. The latter are composed of unstriated muscular fibres, and are attached to the hair-follicle and to the epidermis. The sebaceous gland lies between the muscle and the hair-follicle.

THE SWEAT.—Sweat is a clear, colourless fluid containing 99 per cent. of water; sodium chloride is the most abundant solid constituent, and traces of protein, fatty acids, and urea may also be present. The secretion of sweat is under the control of the central nervous system, the nerves to the sweat-glands belonging entirely to the sympathetic system. Leaving the spinal cord by the anterior roots, they pass to the ganglia of the lateral sympathetic chain, where they have their cell-stations; from these ganglia non-medullated fibres enter the grey rami, and run with the spinal nerves to their peripheral distribution. Sweating is generally brought about by a rise in the temperature of the body and it usually begins as soon as the temperature of the body rises from 0.5° to 1° C. above the normal. The effective stimulus is the raised temperature of the blood passing through the brain;

sweating may be produced by warming the blood passing through the carotid artery to the brain, even though the temperature of the rest of the body remains unchanged. Sweating may also be produced reflexly by the local application of heat to the skin, so that one arm, if warmed, may sweat, and not the rest of the body. It is not necessarily associated with increased vascularity of the skin, and may occur, even in an amputated and therefore bloodless limb, when the sympathetic fibres are stimulated, while in fever there may be dilatation of the cutaneous vessels without an accompanying secretion of sweat.

SECTION II

HEAT-LOSS CONTROL.—The skin not only protects the delicate underlying structures and serves as a sense-organ, but by means of the secretion of sweat plays an important part in regulating the loss of heat from the body. The loss of heat from the skin takes place by radiation, conduction, convection, and evaporation. In *radiation*, heat-waves pass into the air in all directions; in *conduction*, heat is transferred to substances, such as clothing in contact with the skin; *convection* signifies the movement of warmed air by air currents surrounding the body. The loss taking place as a result of these processes is greater when the blood-vessels of the skin are dilated and the skin is flushed than when the vessels are constricted.

More important than any of these is the loss of heat by the *evaporation* of sweat, which is continually being formed on the surface of the skin. When the amount of sweat is small, it evaporates so quickly as to be unnoticed, the process being called *insensible perspiration*. When the amount formed is increased, or its immediate evaporation is prevented, it becomes visible on the surface of the skin as *sensible perspiration*. In the process of evaporation over 580 small calories become latent for every gramme of water converted into vapour, and are lost to the body; and the rate at which this loss takes place may be increased either by greater formation of sweat or by hastening the rate of evaporation by exposing the body to a current of air. Conversely, the loss of heat in this way is checked when an individual is surrounded by air which is already nearly saturated with moisture. Owing to the heat taken up by water as it evaporates, heat continues to be lost by the evaporation of sweat even when the temperature of the surrounding air is higher than that of the body, provided the air is dry. In tropical climates the loss of heat from the skin takes place chiefly by evaporation.

When sweating is profuse the amount of heat lost by the skin

relatively to that lost through the lungs is increased, whereas when the skin is cold and perspiration is scanty the reverse is the case. In dogs, in which, owing to their hairy coat and paucity of sweat-glands, loss of heat by evaporation is comparatively slight, an increase in the loss of heat is largely effected by increased respiratory movements.

HEAT-PRODUCTION CONTROL.—The maintenance of a constant temperature in warm-blooded animals is effected by an exact adjustment through the central nervous system of the production and loss of heat. That the production of heat takes place mainly in the muscles and is under the control of the central nervous system is shown by two observations: (1) When the motor nerve-endings are paralysed by curare so that the muscles are cut off from nervous influences, the animal behaves like a cold-blooded animal. (2) When the spinal cord is injured in man or in the lower animals in such a way that the lower part of the body no longer receives impulses from the brain, this portion becomes poikilothermic, and when it is warmed, its metabolism becomes more active; the heat produced warms the blood passing through it, and may be sufficient to raise the temperature of the whole body several degrees. When the lower part of the body is cooled, its metabolism is diminished, and the temperature of the whole body may thereby be lowered, in spite of the fact that the rest of the body still possesses its regulative mechanism.

Within moderate limits of external temperature the production of heat during rest varies but little, though it is diminished when the surrounding temperature becomes high. During muscular exercise both heat-production and heat-loss are increased, the production exceeding the loss, so that for a time the temperature rises above the normal level.

The intimate relation between production and loss of heat is also shown in the relationship between production of heat and the size of the animal. The greater loss of heat relative to its weight which occurs in a small animal (p. 420) is met by a correspondingly larger production of heat, with the result that the animal's temperature remains constant. In many animals, including man, the regulative mechanism is not fully developed at birth; and the temperature of the new-born infant falls unless loss of heat is prevented by keeping the child in a warm atmosphere.

THE CORPUS STRIATUM.—The part of the nervous system which regulates the production and loss of heat and keeps the

temperature constant appears to be the corpus striatum. Experiments have been made in which, by an ingenious device, the corpus striatum could be warmed or cooled at will. Cooling of the corpus striatum increased the production and diminished the loss of heat; warming had the opposite effect. In the normal animal the temperature of the corpus striatum depends upon that of the blood flowing through it. When the temperature of the body, and therefore of the blood, rises, the corpus striatum reacts by sending out impulses which lessen the production of heat in the muscles and increase the loss of heat from the skin; conversely, a fall of body temperature increases heat-production (*e.g.* by shivering) and diminishes heat-loss. The mechanism is so perfect that in man the temperature remains constant, whether he lives in the tropics or in the arctic regions, though the adjustment fails when the heat or cold is extreme. When a man is exposed to excessive cold, the temperature gradually falls till consciousness is lost, and finally death supervenes.

HEAT-STROKE.—When the surrounding temperature is extremely high, and particularly if loss of heat by sweating is interfered with, the temperature of the body rises very considerably, producing the condition of *heat-stroke*. This occurs more readily if the production of heat is also increased, for example by muscular exercise, or if the evaporation of sweat is checked by a humid atmosphere; in these circumstances the regulative mechanism may fail even though the surrounding temperature is not very high. The treatment of heat-stroke is to give rest to the body as a whole, to bring down the body temperature and to replace the exhausted sweat mechanism by an artificial one. The man is therefore put to bed on a fluid diet. He is covered by a sheet continually moistened with water. Over this a current of air is passed. The fluid evaporates from the sheet, thus cooling it, and this in turn cools the man.

FEVER.—In fever the temperature of the body is raised, the regulative mechanism again bringing about a balance between production and loss of heat, but at a higher level than in the normal person. Owing to the raised temperature of the body, metabolism is more rapid, the breaking down of the tissues is increased, the output of nitrogen in the urine rises, and a loss of weight generally takes place. The raising of the body temperature should be assisted by, *e.g.*, hot-water bottles, since the process is a beneficial one. Only if the temperature rises excessively should any artificial means be employed for bringing the temperature down, *e.g.* cold sponging.

SECTION III

VENTILATION.—Various theories have been advanced to explain the difference between well- and ill-ventilated conditions.

(1) *Oxygen deficiency*: There is ample experimental evidence that men can live for years in good health at high altitudes, where the pressure of oxygen in the air may only be two-thirds the normal amount. In enclosed premises such an oxygen deficiency is never met with. Analyses have shown that a badly crowded room suffers an oxygen deficiency of approximately 1 or 2 per cent. only, whereas at high altitudes deficiency may be as much as 7 or 8 per cent.

(2) *Excess of CO₂*: Experiments indicate quite clearly that breathing air to which 2 or 3 per cent. of CO₂ has purposely been added causes deeper respiration than usual, but no ill effects whatever.

(3) *Protein poisoning*: The protein poisoning hypothesis was advanced on the idea that people in a crowded space poisoned one another with protein material, *e.g.* mucus exhaled in the breath or proteins shed from the skin, thus setting up in one another a species of anaphylactic shock. Careful experiments on rats and guinea-pigs confined in a small space, but with suitable food and under conditions of scrupulous cleanliness, showed that no ill effects whatsoever resulted.

(4) *Odours*: In the same way odours have been found to produce no ill effects on workpeople who are subjected to them year in and year out.

(5) *Moisture*: That moisture is probably one of the important factors is shown by the following experiment: a man at a temperature of 85° Fahrenheit suffers not the slightest inconvenience so long as the air is dry. If, however, the moisture of the air is allowed to rise the conditions become increasingly deleterious until, when the atmosphere becomes 90 per cent. saturated, definite discomfort is experienced. But if this same air be now vigorously stirred, *e.g.* by means of an electric fan, the discomfort immediately disappears, but it reappears again immediately stagnation of the air takes place. Air movement is clearly seen to be an important factor in ventilation (Leonard Hill).

Without going further into details, we may lay down very briefly the rules of good ventilation. Each adult should have a room space of not less than 1000 cubic feet. Some provision should be made for causing this air to be changed two or three times in the twenty-four hours. Under these conditions the CO₂ in the air should never be found to rise as high as 0.1 per

cent. In summer suitable arrangements should be made for keeping this air in motion, particularly if the air be charged with water-vapour. During winter there should be some means of warming either the air in the room, or the man, or both. Experience points to radiant heat as being more satisfactory than convection-carried heat, *i.e.* that it is preferable to warm the man and his surroundings by an open fire, a gas fire, or an electric radiator, rather than by heating the air in the room by means of hot pipes. Special care should be taken not to pass too rapidly from warmed premises to very cold outside air, because this causes the mucous membrane which has become flushed in the warm room to be suddenly chilled and to have its arterial supply cut off while its capillaries are still dilated; the result is a blue mucous membrane which corresponds exactly in its genesis to that of a blue skin. A few minutes in an intermediate temperature would permit drainage of the mucous membrane to take place, that is, its capillaries would return to their normal size; then if a cutting off of the arterial supply takes place on going into the cold air no harm will result.

CHAPTER XX

THE LIVER

SECTION I

THE LIVER is the largest gland in the body. It consists of an enormous number of lobules, each having a diameter of about 1 mm.; they are roughly pear-shaped, and show facets on the surface from mutual compression of adjacent lobules. The narrow end of the pear is the point of emergence of a vein, the *intralobular* vein, which occupies the centre of a transverse section of the lobule. The substance of the lobule is composed of columns of cells, arranged radially in relation to the intralobular vein. The portal vein and hepatic artery enter, and the bile-duct emerges from the liver at the hilum. The three structures have a sheath of connective tissue, known as *Glisson's capsule*, the whole forming the *portal tract*. The portal tract branches in a tree-like manner, the smallest divisions being interlobular. From the interlobular branches of the portal vein blood passes to the intralobular vein in each lobule through sinusoids, which lie between the columns of liver-cells. The sinusoids are wider than capillaries, and their walls are incomplete. The hepatic artery also opens into the sinusoids, supplying oxygenated blood for the nutrition of the liver-cells. The intralobular vein opens into a *sublobular* vein,



FIG. 178.—Section of a lobule of a rabbit's liver, stained with iodine. Glycogen stained reddish-brown. $\times 50$.

and the sublobular veins unite to form the tributaries of the hepatic vein.

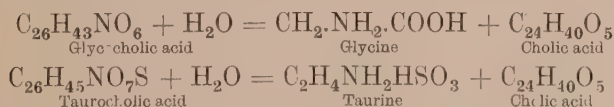
A liver-cell is roughly cubical in shape and contains a large spherical nucleus. Its protoplasm is granular, and in the well-fed animal contains small masses of glycogen, which in the fresh or alcohol-hardened liver can be stained brown with iodine (Fig. 178). The cell contains iron in organic combination; this can be demonstrated by treating the liver with dilute hydrochloric acid and ferrocyanide of potassium, a blue colour being produced. Small droplets of fat may also be present in the cells. Each cell is penetrated by fine canaliculi continuous with the bile-capillaries, and cavities are also described which communicate with the sinusoids. On the side of each cell applied to the adjacent cell is a channel, which, with a corresponding channel on the neighbouring cell, forms a bile-capillary. The bile-capillaries form a network, the contents of which flow into the small bile-ducts at the periphery of the lobule. The ducts are lined by cubical epithelium.

SECTION II

BILE-PIGMENT EXCRETION.—The old view with regard to the origin of the bile-pigments was that they were formed by the liver-cells from hæmoglobin which had been liberated as the result of the breaking down of the red blood-corpuscles, such breaking down having been effected in the spleen or in the hæmolymp glands. Large cells were seen in these organs which were stated to contain disintegrating red blood-corpuscles. The modern view is, however, that the disintegration of the red cells, the liberation of the hæmoglobin and the turning of the hæmoglobin into bile-pigments, or some chemical substance very closely related to the bile-pigments, are carried out by the reticulo-endothelial system. Since the Kupffer cells of the liver are representatives of this system they would have the power of attacking red cells, liberating and changing their contents to bile-pigment: but so, also, would all the other cells which represent this system. The appearance of bile-pigments in the bile points then to little more than their collection by the liver after they have been liberated into the blood-stream. The chemical aspect of bile-pigment formation is somewhat clearer. Test-tube experiments have shown that the transformation from hæmoglobin is quite simple. First, the cleavage of hæmoglobin into hæmochromogen and globin. Then the removal of the iron from the hæmochromogen with the formation of some porphyrin-like body. This by reduction can be transformed into bilirubin, which on oxidation forms biliverdin.

Two facts, which have been known for many years, seem to fit in very well with either view of bile-pigment formation. (1) Injection of hæmoglobin into the blood-stream of an animal, or a substance which will liberate a portion of the animal's own hæmoglobin, results in an increased production of bile-pigment. (2) A large amount of the iron which is liberated from the hæmoglobin as the result of the bile-pigment formation is stored in the liver. As mentioned above, granules of it can be demonstrated there.

THE BILIARY FUNCTION.—References have already been made to this important function of the liver. (See Chapter XV, p. 376). The chemical composition of bile has also been indicated there. Briefly the solid constituents are the bile-salts, sodium taurocholate and sodium glycocholate (the latter of which is usually the more plentiful in gall-bladder bile), the lipines, cholesterol and lecithin, some mucin, traces of fat and soaps, organic salts and the bile-pigments, which we have referred to in Section II above. Of these constituents the bile-salts are from the point of view of digestion by far the most important. Not only do they lower surface tension, thus breaking down those surface barriers that might prevent the enzymes of the intestinal tract from getting into really intimate contact with the cell content of the food, but in addition they play a highly important part in the digestion of fat, as is shown by the large amount which leaves the body undigested when bile is absent (Mellanby). Lastly, by assisting the entrance of secretin into the blood-stream, they stimulate the pancreas to secrete its highly important enzymes. The chemical nature of the bile-salts is well known. They consist of the sodium compounds of glycocholic and taurocholic acids respectively, glycocholic acid being composed of one molecule of glycine combined with cholic acid, and taurocholic acid being the corresponding taurine compound, as is shown by the following formulæ :—



Two tests for these substances may be given : if a little cane-sugar syrup be added to the bile-salts in a test-tube and strong sulphuric acid poured down the side so that it runs below the solution without mixing, a cherry-red colour appears at the

junction of the two fluids. The second test is to sprinkle flowers of sulphur on the solution which is suspected of containing the bile-salts. If they are present the sulphur will sink, owing to the reduction of surface tension which the bile-salts have brought about.

Very little is known of the origin of the bile-salts. The simple amino-acid glycine is readily manufactured in the liver. Taurine may be similarly produced from cystine ($\text{CH}_2\text{SH}.\text{CHNH}_2.\text{COOH}$). The cholic acid may possibly be derived by breaking down cholesterol.

The bile-salts are normally reabsorbed with the digestive products they have helped to form. On entering the bloodstream they recirculate to the liver, are eliminated once more by the liver-cells and are thus utilised over and over again. They probably assist fats and lipines to obtain entry at the same time that they themselves are reabsorbed.

The cholesterol and lecithin of bile are also thought to undergo a similar cyclic process of excretion and reabsorption to that undergone by the bile-salts. Their function in the bile is not known. The mucin, which is replaced by nucleo-protein in ox bile, is derived from mucus-secreting cells which line the bile-ducts and gall-bladder.

SECTION III

DEAMINATION OF PROTEINS.—It has been pointed out in Chapter I that the proteins of the foodstuffs contain amino-acids very nearly similar to those of our own bodies, but the quantities in which the different amino-acids are present vary very greatly. This important subject has already been referred to in Chapter XVI. It should be noted that considerably more protein food has to be provided in the diet than will replace the exact amount of protein lost by the body as the result of wear and tear. If the various amino-acids could be readily converted one into another no excess would have to be given, but some of the most essential of them cannot be so converted. In order that the body's loss of these essential amino-acids should be made good, the diet must contain at least this amount of the amino-acids in question. This means that there will be a large excess of other amino-acids which are present in the food in greater quantities than can be used by the body. It has long been known that these unwanted amino-acids are excreted ultimately as urea by the kidney, but the precise changes which led to the production of the urea were not too clear, nor was it precisely known where the various changes occurred. There is

now, however, proof that the liver is responsible both for deaminating the unwanted amino-acids and for converting the NH_2 groups which are thus split off into urea. With regard to the first process the following evidence may be advanced. If the kidneys be removed from an animal and the blood urea be periodically analysed it will be found that there is a continuous increase until the animal dies in uræmic coma. If, however, at some previous stage the liver also be removed it is found that the urea stays at that level which was reached just prior to the operation, *i.e.* the urea formation ceases at the same moment that the liver function ceases (Mann). It is clear from this that no other organ is concerned with urea production.

The NH_2 groups split off are converted into urea in the following stages: (1) by union with the CO_2 circulating in the blood ammonium carbonate is formed; (2) by the loss of one molecule of water, this is converted into ammonium carbamate; and (3) by the loss of a further molecule of water ammonium carbamide urea is produced. Evidence for these stages is the fact that an increased hydrogen ion concentration of the blood causes a demonstrable increase in the ammonium salts of the blood. The result is that ammonium compounds appear in the urine in place of urea. Thus it is only necessary to inject a mineral acid into the blood-stream of an animal to find subsequently a quantitative decrease in the amount of urea and a quantitative increase in the ammonium compounds in the urine. Further, the perfusion of ammonium carbonate or ammonium carbamate through the excised liver in suitable circumstances is found to lead to the formation of urea. It is not only the proteins which have entered the body as food which are deaminated in this way. There is ample evidence that the body's own proteins are treated in a similar manner during starvation. Whereas 30 grammes of urea may be excreted on an ordinary diet, the whole of which may have come from the unwanted amino-acids of the food, during starvation 13 grammes of urea may be excreted as a result of the deamination of the body's own proteins, the object being to provide the necessary fuel by disintegrating this amount of protein.

DESATURATION OF FATS.—The fact that fats form an important part of the dietary and that they can replace an equivalent amount of carbohydrate has been strong evidence for the breaking down of the fats into simpler substances so that they could be oxidised readily to their complete breakdown

products of carbon dioxide and water. But it has not been known through precisely what stages the fats passed in this breakdown process. Now, however, there is proof that one of the functions of the liver is to break off from the fats some of the hydrogens which form the side-chains. In consequence, whereas food fat as a rule contains olein as the single unsaturated fat, the fat-depôts of the body contain increased amounts of unsaturated fats, and these are of a lower series than those usually found in the food. Thus it is possible to find in the fat-depôts fats which have lost as many as four hydrogen atoms. When the liver-cells are extracted with fat solvents and the resulting products analysed, it is found that the fats there are frequently of a very unsaturated kind. This points to the liver as the source of the unsaturated fats. The desaturation is apparently the first stage, the second stage being the breaking up of the fatty chains into short lengths. These short lengths are then dealt with piecemeal with the oxygenation of the molecules which compose them. There is some evidence that lecithin, and possibly cholesterol, can be formed by the liver from the ordinary fats of the diet. An alternative view is, however, that this transformation occurs during absorption through the intestinal wall. Both views may be correct.

THE GLYCOGENIC FUNCTION.—Claude Bernard was the discoverer of the glycogenic function of the liver. His discovery was quickly followed by the working out in detail of the way that carbohydrate taken in a food passed in the portal blood to storage in the liver to be released as and when required for the utilisation of the tissues. In this way the older physiologist pictured the blood-sugar level being kept constant. Further knowledge resulted from a detailed examination of the processes occurring in diabetes, and the importance of the islet tissue in the pancreas to the glycogenic functions of the liver became emphasised. Some facts have, however, recently come to light which show that in diabetes it is the liver which breaks down the tissues' own proteins, producing urea on the one hand and carbohydrate, which it pours into the circulation, on the other. Since the tissues are unable to use the carbohydrate thus presented to them, this activity on the part of the liver is entirely superfluous. In normal circumstances the state of affairs is very different, for the carbohydrate thus formed by protein deamination may either be passed into the blood or, if this be adequate, it may be stored as glycogen by the liver. Whereas insulin causes the

liver to store glycogen, the administration of adrenaline, pituitrin, and thyroxin bring about the opposite result. Thus, puncture of the floor of the fourth ventricle, which was discovered by Claude Bernard to result in mobilisation of the liver glycogen and the appearance of considerable quantities of sugar in the urine, appears to be due to the liberation of adrenaline by the adrenal glands, the stimulus passing down to them by the splanchnic nerves.

SECTION IV

HEPARIN PRODUCTION.—The rôle of the liver in preventing the coagulation of the blood has already been referred to in some detail in Chapter IV. It will be remembered that the injection of peptone into the circulation of an animal results in its blood becoming non-coagulable. Removal of the liver prevents peptone having this effect, which shows clearly that the peptone has stimulated the liver-cells in some way to produce a substance which prevents coagulation. This used to be called antithrombin, but is now called heparin. There is evidence that this substance is normally produced by the liver in order to prevent any spontaneous coagulation occurring in the blood in the vessels. Hence it has been inferred that small quantities of cephalin are continually being produced by the blood and that this heparin is necessary to neutralise its effects. Pure preparations of heparin have been prepared. It is soluble in water, is non-toxic, and is thought to consist of a combination of glycuronic acid and carbohydrate. Howell believes that it combines or reacts with prothrombin (thrombogen), thus preventing its activation to thrombin.

OTHER FUNCTIONS OF THE LIVER.—In common with most of the large organs the liver plays an important part in red blood-corpuscle formation in the young animal. The blood sinuses which exist between the liver-cells are filled with megalo-blasts which are producing nucleated and non-nucleated red blood-corpuscles,

THE DETOXICATION OF POISONS.—Besides dealing with the products of protein breakdown, indole, scatole, and phenol, with the formation of indoxyl sulphate, scatoxyl sulphate, and phenyl sulphate, it is now known that the liver deals with a number of poisons both of bacterial origin and otherwise. In addition, the

Kupffer cells are actively phagocytic and remove foreign particles from the blood-stream.

We have already referred in Chapter XVIII to the fact that both Vitamins A and D are found in fats of animal origin, particularly in liver fats. It is not only cod liver that is rich in these important vitamins ; they are also said to be present in the human liver.

Lastly, the heat production in the liver must be referred to. Owing probably to the magnitude of the chemical changes which the liver-cells carry out, some of which have been referred to briefly in the above sections, a considerable production of heat takes place and, in consequence, the blood leaving the liver is frequently found to be as much as a degree hotter than the blood going to it.

The liver has been found to play an important part in curing pernicious anæmia. The blood picture of this disease may be described as follows : (1) The red cells are too few and are abnormal in size and shape. The hæmoglobin content of the cells is normal or actually increased. (2) The white cells are decreased in number. (3) The platelets are reduced in number. The signs are : (1) reduced HCl in gastric juice, and (2) increased bile-pigments in the blood. The immediate cause seems to be increased red (and white) cell destruction. This explains the excess of bile-pigments, but not the reduced HCl. Liver feeding or the administration of liver extracts very rapidly improves the condition of patients until they are cured.

CHAPTER XXI

THE URINARY SYSTEM

SECTION I

THE KIDNEY.—This organ performs two most important functions: (1) it eliminates waste products such as urea and uric acid; (2) it adjusts with the greatest precision the chemical composition of the plasma. It also probably controls the volume of the blood-plasma.

THE HISTOLOGY OF THE KIDNEY.—The kidney is a compound tubular gland having a duct, the ureter, which connects it with the bladder and is expanded at its upper end to form the pelvis of the kidney. On dividing the kidney lengthwise from its outer to its inner border, it is seen to consist of two layers, an outer reddish-brown *cortex*, and an inner pale *medulla*. The latter is composed of a number of pyramids, the apices of which project as papillæ into the pelvis of the kidney. The larger subdivisions of the renal artery and vein lie between the cortex and medulla, this region being known as the *boundary zone*. Prolongations of the medullary tissue extend radially into the cortex, forming the medullary rays.

The kidney consists of a mass of tubules, held together by connective tissue. Each tubule begins in the cortex by a blind expanded end (Bowman's capsule), which may be compared with a small ball indented so that its opposing walls almost touch; the capsule consists of a single layer of squamous epithelium. A bunch of capillaries, known as a *glomerulus*, projects into the indentation. At the pole opposite the entrance of the blood-vessels Bowman's capsule opens into the tubule proper, which at first takes a tortuous course and is known as the *first convoluted tubule*; it then becomes spiral or nearly straight (*spiral tubule*), passes into the medulla, where it forms a loop (*loop of Henle*) and returns into the cortex. Here it becomes irregular and angular (*zigzag tubule*), and then convoluted (*second convoluted tubule*), and ultimately joins a straight *collecting tubule* (Fig. 179). The collecting tubules

run into the medulla, and open at the apices of the pyramids into the pelvis of the kidney.

The convoluted, spiral and zigzag tubules are lined by columnar or cubical cells, the lateral surfaces of which dovetail into each other; the cells are very granular, the granules tending to be

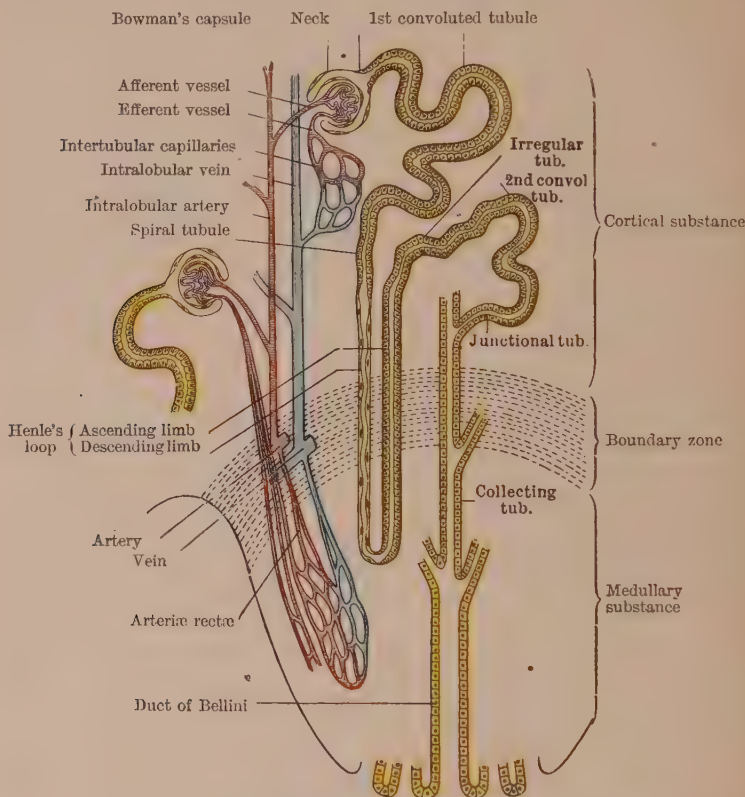


FIG. 179.—Scheme of a renal tubule and its vascular supply.
(From Gray's *Anatomy*.)

arranged in rows at right angles to the lumen, so that the cells have a rod-like appearance. The descending part of the loop of Henle is lined by clear, flattened epithelium; the cells of the ascending limb resemble those of the convoluted tubules. The collecting tubules are lined by clear, cubical cells. Throughout the whole length of the tubules the cells rest upon a well-marked basement-membrane.

THE BLOOD-SUPPLY.—The distribution of the larger blood-vessels in the kidney is best seen if the vessels are injected

with a medium containing a barium salt, and an X-ray photograph of the kidney is taken. The arrangement of the smaller vessels is demonstrable by the usual histological injection technique. The renal artery enters the kidney close to the origin of the ureter and divides into "interlobar" branches, which lie in the boundary zone between the cortex and the medulla. From those vessels smaller branches pass outwards, and give off straight intralobular arteries directed towards the surface of the kidney. The intralobular arteries give off short afferent vessels, one to each adjacent glomerulus. The blood leaves the capillaries of the glomerulus by an efferent vessel, which is smaller than the afferent and, after a short course, breaks up into a second set of capillaries round the convoluted tubules; from these capillaries the blood passes into veins opening into the larger veins in the boundary zone. The veins ultimately unite to form the renal vein. Branches also arise from the larger arteries to end in capillaries round the tubules in the medulla; from these the blood passes back to the corresponding veins.

THE VOLUME CONTROL OF THE KIDNEY.—One of the important functions of the kidney appears to be the precise control of the blood-volume, or possibly it would be more correct to say the plasma-volume. Suppose for example that a man drinks a salt solution which is isotonic with his plasma: the result is a secretion by the kidney of urine in excess of the amount in an equivalent normal period. The salt concentration of this urine corresponds fairly closely with that of the salt solution which was consumed, and this secretion goes on until the plasma-volume has returned to its normal value. When, however, a man suffers a loss of blood, the volume of urine secreted is markedly below normal and analysis of the secreted urine shows that the kidney is attempting to excrete the metabolites, *e.g.* urea and uric acid, with the accompanying secretion of the smallest quantity of water and salts. This it continues to do until by drinking water or otherwise the lost fluid is made good. If, after such a hæmorrhage, a blood transfusion is effected and normal blood in excess of that required is put into the circulation, then the kidney rapidly excretes the excess fluid until the blood-volume is restored to its normal amount. This will leave an excess of corpuscles, but the reticulo-endothelial system, *e.g.* the Kupffer cells of the liver, then deal with the situation so that in a few days the number of corpuscles per cubic millimetre of blood is restored to the normal.

THE OSMOTIC CONTROL OF THE KIDNEY.—Reference has already been made in Chapter I to the importance of correct

salt concentration in the blood, so that the osmotic pressure at the tissues shall always be at approximately the normal value. This osmotic relation is continually being disturbed by various factors. For example, drinking fluid the salt content of which is low, *e.g.* water, or consuming a diet which contains insufficient salt, or living under conditions which make the amount of fluid perspired by the skin low, will clearly cause the osmotic pressure of salts in the blood to diminish; on the other hand, insufficient fluid in the diet, or excess of salts in the diet, or living in conditions where much perspiration is produced, will cause the osmotic pressure to rise above the normal. The kidney is continually dealing with such situations. Experiment shows that it deals with each case in the most appropriate way. Thus, if the osmotic pressure falls and the blood-volume is maintained, a watery urine is excreted in moderate amounts. On the contrary, if the osmotic pressure falls and the blood-volume correspondingly increases (as would happen, for example, if a man consumed a large quantity of water), then the kidney excretes a large volume of urine of which the salt concentration is low. In the same way, a rise in the osmotic pressure above the normal, accompanied by no increase in blood-volume, leads to the secretion of small quantities of urine with a very high salt concentration. If the osmotic pressure be raised and the blood-volume increased at the same time, the result is the excretion of a large amount of urine in which the salt concentration is above the normal. In each instance the kidney does its best to adapt itself to the circumstances which are obtaining at the time.

THE SALT CONTROL OF THE KIDNEYS.—Experiment shows that just as the osmotic pressure of the blood remains approximately constant, so also does the concentration of the individual salts in the blood-plasma. Thus we may purposely abstain from taking sodium chloride and substitute sodium bromide instead, and we would find that, although a temporary fall in the chloride content of the plasma may take place, bromide being substituted, this is very quickly rectified on returning sodium chloride to the diet again. The same is true of any other salts which we care to substitute. The kidney tries consistently to retain in the plasma those constituents which the plasma normally contains, and secretes as rapidly as possible those salts which are foreign to it or are present in an abnormal concentration. The kidney appears to deal with each separate ion and anion as if it alone were the substance dealt with, and it preserves each at its appropriate concentration.

THE H ION CONTROL OF THE KIDNEY.—The importance of correct hydrogen ion concentration of the blood has been emphasised in Chapter I. When the H ion concentration of the blood is disturbed the first effect is on the respiratory centre. Thus, if the H ion concentration of the blood increases, the respiratory centre is stimulated and increased quantities of CO_2 are excreted, so that the H ion concentration of the blood is returned to the normal. But if the blood becomes too basic, respiratory movements decrease in intensity, and CO_2 tends to accumulate until the normal H ion concentration of the blood is restored. The lungs effect a temporary restoration only; it remains for the kidney to finish the work that the lung has begun. When the blood becomes too acid and in consequence CO_2 is turned out by the kidneys, then acid substances are left in chemical combination with the base with which the CO_2 was previously in combination. Suppose, for example, that dilute sulphuric acid were consumed. This would pass through the bowel-wall into the blood and would combine with the sodium bicarbonate there with the production of sodium sulphate. CO_2 would be passed out by the lungs into the air, but normal conditions would only be restored when the kidneys had excreted the sodium sulphate. Experiment shows that excretion of this foreign salt by the kidney is quickly effected.

The H ion concentration of the blood is in normal circumstances increased by free acids taken in with the diet. It is also increased when the alkali of the blood is combined with lactic acid set free in the muscles as the result of active exercise. The blood becomes more acid during the excretion of alkali into the small intestine during the production of the pancreatic and biliary secretions. It also becomes more acid during protein digestion when the amino-acids and the phosphoric acid, which results from purin metabolism, are finding their way into the blood. Lastly, it tends to become acid when in starvation the body's own proteins are being broken down, and in consequence sulphur and phosphorous compounds are being oxidised with the production of their respective acids. Under all these conditions the immediate result is to increase the activity of the respiratory centre and to readjust temporarily the H ion concentration of the blood by a suitable excretion of CO_2 . The kidney thenceforward turns out a urine which contains more acid sodium phosphate than alkaline sodium phosphate, and this goes on until the normal salt balance of the blood has been restored. If salts of foreign acids have entered the blood, such as sodium sulphate, these are of course excreted.

Under the reverse conditions the blood may become too

alkaline. A vegetable diet always contains considerable quantities of sodium and potassium salts of weak organic acids such as citric and tartaric. The latter are readily oxidised in the body, leaving the bases free to cause increased alkalinity in the blood. When acid is being produced by the stomach during gastric digestion the blood temporarily becomes alkaline. Further, when muscular exercise is over and the lactic acid which has temporarily been stored in the blood in combination with some of the bases is being built back again into the muscles from which it started, this base is left free and temporarily causes alkalinity of the blood. In all these instances the immediate result is diminished activity on the part of the respiratory centre, so that CO_2 accumulates in the blood and combines with the alkalies present until the normal reaction of the blood is restored. Then the kidney takes on its share of the work and excretes the unwanted salts which have resulted, until the normal salt balance is re-established.

If the blood remains persistently acid in spite of the efforts of the respiratory centre and kidney to deal with the situation in the normal way, two further lines of defence are available. As has been mentioned before, a part of the urea may be excreted in the form of ammonium salts combined with whatever acid is producing the acidity of the blood, but calcium salts may be excreted as well, the calcium being that taken in with the food, which in normal circumstances would be excreted with the fæces as earthy calcium salts. The appearance of ammonium compounds and calcium compounds is, therefore, an indication that the amount of available base in the blood is becoming curtailed.

SECTION II

THE NITROGENOUS EXCRETORY FUNCTION.—That this function is a highly important one is at once shown by examples of its failure. If the products of protein metabolism are not rapidly excreted, “uræmic coma” supervenes. There is weakness, loss of appetite, and drowsiness. The drowsiness gets progressively worse and death follows about seven days from the onset of the renal failure.

THE TOTAL NITROGEN IN URINE.—This is estimated by *Kjeldahl's method*. A known volume of urine is boiled with pure sulphuric acid until all its carbon is fully oxidised, the nitrogen being converted into ammonia, which combines with the acid. The solution is then made alkaline with caustic potash, the ammonia which distils off being collected in a known volume of one-tenth normal sulphuric acid. The amount of acid neutralised

by the ammonia is determined by subsequent titration of the uncombined acid with one-tenth of normal caustic potash.

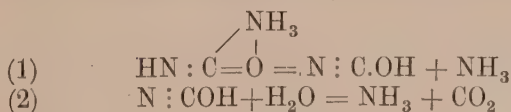
From the measurement of the total nitrogen in urine the quantity of protein in the diet may be estimated, since on the average 6.25 grammes of protein contain 1 gramme of nitrogen. Suppose, for example, 21 grammes of nitrogen were excreted per day. Roughly, 1 gramme of this being due to the breakdown of body proteins (endogenous), 20 grammes of nitrogen represent the protein in the food. The weight of this equals $20 \times 6.25 = 125$ grammes per diem. Of this 20 grammes of nitrogen, about 85 per cent. (= 17.5 grammes) is due to urea. Since the nitrogen represents a little over half the weight of the urea, the daily excretion of urea is about 33 grammes.

UREA.—Urea, $\text{CO}(\text{NH}_2)_2$, is a solid, crystallising in colourless rhombic prisms which are easily soluble in water, alcohol, and acetone. When heated, the crystals decompose, giving off ammonia and yielding a body called *biuret*. To estimate the amount of urea in urine, treat a known volume of urine with an extract of soya bean, which converts urea into ammonia; the ammonia formed is aspirated into a known volume of one-tenth normal acid, and the amount of uncombined acid is subsequently estimated by titration with one-tenth normal caustic soda. The action of the soya bean is due to a ferment known as urease.

Urea is the most abundant nitrogenous constituent of urine, its amount varying, as seen in the table on p. 462, with the quantity of protein food consumed; in starvation, urea is derived entirely from the breaking down of the tissue-proteins.

Recent research suggests that the structural formula for urea may be $\text{HN} : \text{C} \begin{array}{l} \swarrow \text{NH}_3 \\ | \\ \text{O} \end{array}$ which agrees better with many of its re-

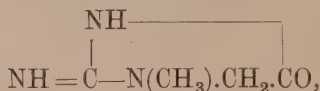
actions than the usual formula. Thus, urease converts it first into cyanic acid and ammonia which then yields CO_2 and NH_3 :—



AMMONIA.—The ammonia normally found in the urine represents the small amount which escapes conversion into urea by the liver, and is but little affected by the amount of protein in the diet. In some abnormal states acids formed in the body combine to a large extent with ammonia in the blood, being

excreted as ammonium salts in the urine, and the amount of urea is correspondingly diminished. The amount of nitrogen excreted as ammonia in these circumstances is sometimes 20 per cent. or more of the total urinary nitrogen.

CREATININE AND CREATINE.—Creatinine is an anhydride of creatine, which occurs in muscle as creatine phosphate (phosphagen), and may be formed from creatine by boiling with strong hydrochloric acid. It has the formula



and gives a red colour with caustic potash and picric acid (Jaffe's test). It is derived solely from the endogenous metabolism of protein; the amount excreted in the urine by the same person from day to day is remarkably constant, and serves as an accurate index of the extent of endogenous protein metabolism.

The origin of creatinine and its relation to the creatine present in muscle are not fully understood, though creatinine appears in the urine in increased amount in fever, and in other conditions of rapid wasting of muscular tissues. Creatine also, though not usually present in the urine of adults, is found in traces during starvation, in diabetes, in acute fevers, and in women during involution of the uterus. Aceto-acetic acid may be present in the urine under all these conditions, and care must be taken to remove it before estimating creatine, since its presence interferes with the determination. It is possible that normally the creatinine in the urine is formed from creatine, and that in the conditions just mentioned an increased amount of creatine is set free by decomposition of protein, some of it being converted into creatinine, while a portion is excreted in an unaltered form. If a small quantity of creatine is ingested, however, it is entirely oxidised in the body. If a larger quantity is eaten, some appears unchanged in the urine.

URIC ACID exists in urine in the form of mono-urates. On adding strong hydrochloric acid to urine and allowing it to stand for twenty-four hours, uric acid separates out as small pigmented crystals of a characteristic whetstone shape (Fig. 180). Uric acid itself is colourless, but it usually carries down uroerythrin when it is deposited in urine. It is almost completely insoluble in water, but dissolves in weak alkalis. It slightly reduces Fehling's solution (p. 465), and will also reduce an alkaline solution of silver nitrate (Schiff's test). A solution of uric acid,

when evaporated to dryness with nitric acid at a moderate temperature, yields a purple colour on the subsequent addition of ammonia (murexide test).

Roughly, half the uric acid in urine is derived from the nuclein in food and half from the breaking down of the nucleins of the tissues. In addition to uric acid, small amounts of the purine bases are found in urine.

HIPPURIC ACID.—This is synthesised in the kidney, and possibly in the liver, from benzoic acid and glycine, the synthesis being brought about by an enzyme. It is the only normal urinary constituent which is formed in the kidney itself. The synthesis can be brought about *in vitro* by mixing minced kidney, or liver, with benzoic acid and glycine, and keeping the mixture at body-temperature for a time. It will not occur if the kidney-cells are destroyed, for instance, by grinding them with sand.



FIG. 180.—Deposit of uric acid. (After Funke.) (From Plimmer's *Practical Organic and Bio-Chemistry*.)

SULPHATES.—The sulphates are of two kinds: (1) inorganic and (2) ethereal. The latter are compounds of sulphuric acid with phenol, indoxyl, or skatoxyl, and potassium. Indole and skatole are formed from tryptophane by bacterial action in the digestive tract; and, after absorption into the blood, they are first converted by oxidation into indoxyl and skatoxyl, and then combined with sulphuric acid, in the liver, and excreted by the kidneys. Phenol, also, is a product of decomposition of protein. As a rule the ethereal sulphates form about one-tenth of the total sulphates, but when the products of bacterial changes accumulate in the digestive tract (*e.g.* in constipation) or when phenols are given by the mouth, the proportion of ethereal sulphates is increased. Some sulphur is also excreted in organic combination, *e.g.* as traces of cystine or mercaptans, and is known as "neutral" sulphur.

The sulphuric acid of the urinary sulphates is formed almost entirely by the oxidation of the sulphur contained in protein, and the total amount of sulphates varies, therefore, with the quantity of protein food ingested. Soluble sulphates given by the mouth

are partly excreted by the kidneys. Urine also contains *sodium chloride* and *phosphates*, the latter being of two kinds: (1) acid phosphates of sodium, ammonium, and potassium, and (2) earthy phosphates of calcium and magnesium.

SECTION III

COMPOSITION OF NORMAL URINE.—Normal human urine is a clear yellow fluid, acid in reaction, and containing about 4 per cent. of total solids; it is free from cells and from protein, except for a small trace of nucleo-protein derived from the bladder and urinary passages. Its specific gravity varies from 1015 to 1025, and its daily amount is about 1500 c.c. Its average composition is 96 per cent. H_2O and 4 per cent. solids, half of which is urea. The amounts of the various constituents excreted are shown in the following table:—

Total urea	.	.	.	.	33	grammes
„ uric acid	.	.	.	.	0.75	„
„ creatinine	.	.	.	.	1.0	„
„ hippuric acid	.	.	.	.	0.5 to 0.7	„
„ ammonia	.	.	.	.	0.75	„
„ chlorine	.	.	.	.	10.0	„
„ phosphoric acid	.	.	.	.	2.5 to 3.2	„
„ sulphuric acid	.	.	.	.	2.5	„
„ sodium	.	.	.	.	5.0	„
„ potassium	.	.	.	.	4.0	„
„ calcium	.	.	.	.		
„ magnesium	.	.	.	.		

Since nearly all the nitrogenous end-products of the metabolism of protein are excreted in the urine, its composition largely depends upon the quantity of protein food consumed, and on the katabolic changes in the tissue-proteins. The characters of urine vary, therefore, not only in different individuals, but even in the same individual from day to day, and almost from hour to hour.

In addition to solid substances in solution the urine also contains gases. For example, its CO_2 content is about 9 per cent. It also has in it small amounts of nitrogen and oxygen in solution.

AMOUNT AND SPECIFIC GRAVITY.—The fluid taken by the mouth leaves the body partly in the urine and partly through the skin and lungs. In hot weather or during exercise, when evaporation of sweat from the skin is considerable, the urine is decreased in amount and is proportionately concentrated. When the

secretion of sweat is scanty, for example on a cold day, a larger proportion of water is excreted by the kidneys, and the urine is abundant and of low specific gravity; copious draughts of water produce the same effect. In diabetes the presence of sugar may raise the specific gravity to 1040 or more, while in some forms of renal disease the specific gravity is always low (1005 to 1015).

REACTION.—The acid reaction of normal urine is due to acid sodium phosphate (NaH_2PO_4); no free mineral acid is present. The bases and acid radicals mentioned in the foregoing table are combined to form salts, and are derived from the food. Sulphuric and phosphoric acids are formed by the oxidation of the sulphur and phosphorus contained in protein, and, when the food contains much protein, the amount of these acids is increased in the urine, which becomes strongly acid in reaction. Vegetable foods contain organic salts, such as citrates and tartrates of potassium and sodium, in abundance, and in the body these organic acids are completely oxidised, whereas the bases are excreted in the urine. Hence in herbivorous animals, and in man on a vegetarian diet, the urine is neutral or alkaline, though a starving herbivorous animal which is living on its tissue-proteins, and is for the time being carnivorous, excretes an acid urine.

COLOUR.—The colour of urine is almost entirely due to a pigment, *urochrome*, of uncertain origin, the spectrum of which shows no absorption bands. In addition, urine may contain three other pigments, namely, (1) urobilin, (2) uroerythrin, and (3) hæmatoporphyrin.

Urobilin is formed in the digestive tract from bilirubin by bacterial action, and after absorption into the blood is excreted into the urine chiefly as a colourless chromogen, urobilinogen, which is converted into urobilin by oxidation. Urobilin itself occurs in urine in considerable quantity when the amount of bile-pigment formed in the liver is increased by an unusually rapid destruction of red cells in the body, for instance in pernicious anæmia. It shows an absorption band at the junction of the green and blue part of the spectrum, and gives a green fluorescence with zinc chloride and ammonia.

Uroerythrin occurs in combination with deposits of urates, giving them a pink colour, which is changed to green on the addition of an alkali; its composition is unknown.

Hæmatoporphyrin may occur in sulphonal poisoning.

URINARY DEPOSITS.—On standing, normal urine deposits a cloud of mucus derived from the urinary passages. When

the urine is concentrated, *urates of sodium and potassium* are often deposited as an amorphous sediment, coloured pink by uroerythrin, and dissolving when warmed. *Earthy phosphates* are deposited from neutral or alkaline urine: they dissolve on the addition of acetic acid.

Crystalline deposits may also occur in urine, and are usually indicative of abnormal processes taking place either in the body or in the urine itself. The nature of the deposits varies with the reaction of the urine.

In acid urine those most frequently seen are, first, *uric acid* crystals, which assume the form of whetstones or cylinders, and are usually, though not invariably, pigmented; and, second, *calcium oxalate*, occurring as small, colourless octahedra, often called "envelope" crystals from their appearance under the microscope. Uric acid and oxalate crystals are frequently found together. Other crystalline deposits occasionally met with in acid urine are *cystine* (flat hexagonal colourless plates) and the *urates of sodium or ammonium*, which form spheroidal masses with projecting spikes. Under abnormal conditions leucine and tyrosine crystals may also be present. (See later.)

In alkaline urine the crystals most commonly met with are (1) *calcium phosphate*, occurring as prisms arranged in rosettes, and (2) *ammonio-magnesium phosphate*, NH_4MgPO_4 . The latter, often called "triple phosphate," is formed when urine becomes alkaline as a result of the bacterial decomposition of urea; the crystals are large and very characteristic, resembling knife-rests or coffin-lids (Fig. 181). Crystals of calcium carbonate, calcium hydrogen phosphate, ammonium urate, and magnesium phosphate may be met with.



FIG. 181.—Deposit of triple phosphate and ammonium urate. (From Plimmer's *Practical Organic and Bio-Chemistry*.)

COAGULABLE PROTEIN.

Except for a trace of nucleoprotein normal urine contains no protein. In disease of the kidney, serum-globulin and serum-albumin escape from the blood into the urine, and are coagulated on boiling the urine (after the addition of a drop or two of dilute acetic acid). Further, when urine containing protein is poured on to the surface of strong nitric

acid, a precipitate forms at the junction of the two fluids (Heller's test).

SUGAR.—The conditions under which sugar occurs in urine have already been dealt with (p. 406). In man the usual cause of glycosuria is diabetes, and the sugar is glucose. In rare cases the urine contains lævulose or pentose. Lactose is sometimes found during lactation, even in healthy women. The amount of glucose present in the urine in diabetes may vary from mere traces up to 350 to 500 grammes daily.

Glucose reduces alkaline solutions of copper sulphate, yielding cuprous oxide. The solutions generally used in testing for glucose are: (1) Fehling's solution, containing copper sulphate, caustic potash, and Rochelle salt; the latter keeps in solution the cupric hydrate formed by the interaction of the copper sulphate and caustic potash; (2) Benedict's solution, which contains copper sulphate, sodium carbonate, and sodium citrate. Benedict's solution is the more satisfactory, since, unlike Fehling's solution, it is not reduced at all by uric acid or creatinine, nor does it become self-reducing when kept for some time. Other tests for glucose are (1) the preparation of the osazone with phenylhydrazine, and (2) the fermentation test with yeast, which converts glucose into carbon dioxide and alcohol.

The estimation of sugar may be effected by Benedict's method. The solution used contains copper sulphate, sodium carbonate and citrate, potassium thiocyanate, and potassium ferrocyanide. 25 c.c. of the solution and 3 or 4 grammes of anhydrous sodium carbonate are placed in a small flask and boiled. The sugar solution is added from a burette until the blue colour of the reagent disappears; this is the end-point. The thiocyanate forms a *white* precipitate with the cuprous hydroxide formed by the reduction of the copper sulphate, and the end-point is quite sharp. 25 c.c. of the solution are reduced by 0·05 gramme of glucose.

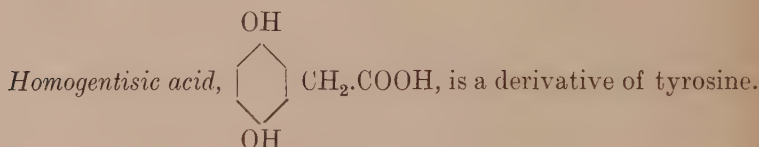
Glycuronic acid ($\text{COOH}(\text{CHOH})_4\text{CHO}$) sometimes occurs in urine, either after the administration of certain drugs, such as chloral, or in combination with indoxyl. It reduces Fehling's and Benedict's solutions and forms an osazone, but may be distinguished from glucose by means of yeast, which does not ferment it.

BILE is present in the urine in jaundice, giving it a greenish or brownish colour; its presence may be recognised by Gmelin's test for bile-pigments or Hay's test for bile-salts.

BLOOD occurs in urine as the result of hæmorrhage in the kidneys or urinary passages, and may be identified by observing the red corpuscles under the microscope, or by spectroscopic examination.

PRODUCTS OF ABNORMAL METABOLISM.—These include β -oxybutyric acid, diacetic acid, and acetone (p. 408); leucine and tyrosine, which are present in acute atrophy of the liver; cystine, and homogentisic acid.

Cystine is set free in the course of the digestion of protein and, after being absorbed, it is normally either oxidised or built up into tissue-protein. In rare cases the cystine escapes oxidation and is excreted as such, and may form crystalline deposits or calculi.



In certain persons the oxidation of tyrosine is incomplete, and stops with the production of homogentisic acid, which appears in the urine. The condition is known as *alcaptonuria*, and the urine darkens on standing and reduces Fehling's solution. In persons suffering from *alcaptonuria* the amount of homogentisic acid in the urine varies from 3 to 6 grammes daily; it is proportional to the quantity of phenylalanine and tyrosine present in the proteins of the food, and is increased when these substances are given as such by the mouth. Thus the whole of the tyrosine and phenylalanine taken into the body is excreted as homogentisic acid. An allied substance, parahydroxyphenylacetic acid, may appear in the urine of normal persons when the passage of the intestinal contents is slow.

Cystinuria and *alcaptonuria*, when they occur, are present at birth and persist through life; they are due to "inborn errors" of metabolism, probably to the lack of certain ferments, and do not lead to any disturbance of health.

Hæmatoporphyrin normally occurs in minute traces. In poisoning by sulphonal it may be present in large amounts.

SECTION IV

THE FORMATION OF URINE.—Broadly speaking, the function of the kidney is to keep the composition of the blood constant by excreting into the urine any excess of substances

normally present in the blood, such as water, sodium chloride, and glucose, or other substances which are not normal constituents of the blood. The abolition of this function by the complete removal of the kidneys leads to the retention of the urinary constituents in the blood, and the man dies in a week.

So far as is known, there are no secretory nerves to the kidney ; its functional activity is excited solely by any alteration in the chemical composition and amount of the blood flowing through it.

The structure of the renal tubule is extremely complex, and many views have been held as to the functions of its different parts. Bowman suggested that the glomeruli filtered off water and salts, the remaining urinary constituents being secreted by the tubules.

Heidenhain regarded both the tubules and glomeruli as possessing a secretory function. Ludwig believed that the whole of the urine was formed by the filtration through the glomeruli of a fluid identical in composition with the blood-plasma minus its proteins, and that, in the passage of this fluid down the lumen of the tubules, much of the water and some of the salts were reabsorbed by diffusion, so that the composition of urine, as it left the kidney, differed greatly from that of blood-plasma. Since blood-plasma contains about 0·02 to 0·05 per cent. of urea, whereas urine contains 2 per cent. of urea, this theory demands that at least 60 litres of fluid should be filtered off daily by the glomeruli, of which all but 1·5 litres are reabsorbed.

CUSHNEY'S THEORY.—The modern view advanced by Cushney is that the function of the glomeruli is to filter off from the blood a fluid identical with plasma minus its proteins. This fluid thus contains small quantities of urea, etc. He holds that the tubules reabsorb from this fluid back into the blood the salts and water, leaving the urea, etc., to be excreted.

TEST I.—Recently Richards and Wearn have by means of a micropipette collected the glomerular fluid in frogs. This when analysed was found to contain much NaCl, some urea and potassium. Sugar was found to be present when it was also found in the blood. Protein was absent. So far Cushney's theory has stood the test of experiment.

TEST II.—According to the theory the NaCl and sugar present in the glomerular fluid should be absorbed back into the blood, while the urea is allowed to pass on to the bladder. Experiment showed that such was the case ; the theory has therefore stood Test II also.

TEST III.—The histological features of the glomeruli and tubules should be in correspondence with what the theory supposes to be their functions. The glomeruli according to the theory are passive filters of fluid. The rate of filtration is increased by increasing the pressure and by decreasing the thickness of filter.

Now the capillary pressure inside the glomerulus is found to be exceedingly high, being only about 20 mm. less than the blood-pressure. Further, the wall of cells between blood and glomerular capsule is extremely thin. That is, both conditions for rapid filtration are present. On the contrary, the tubules have to actively reabsorb. Their cell-walls should be stout and their capillary pressure low. These features also are found. We may say then that Test III is successfully passed.

TEST IV.—If the blood-plasma is filtered through peritoneal membrane soaked in gelatin, it is found that, when the difference of pressure on the two sides of the membrane is 40 mm. Hg or more, the filtrate contains the dissolved constituents of plasma with the exception of protein; with a lower difference of pressure no filtration occurs. This is due to the fact that the proteins in plasma exert an osmotic pressure equal to about 40 mm. Hg, and water tends to pass back by osmosis from the filtrate into the plasma. It is for this reason that the passage of fluid through the glomerular wall ceases when the arterial blood-pressure falls below 40 mm. Hg. If the osmotic pressure of the blood is diminished by decreasing the amount of protein in the plasma, for instance by diluting the plasma, urine may be formed when the blood-pressure is considerably less than 40 mm. Hg. In hydræmic plethora (p. 158), not only is the plasma more dilute, but the renal vessels are dilated and the pressure in the glomeruli is raised; and the formation of urine is accelerated (Fig. 182, B). The difference of pressure on the two sides of the walls of the glomeruli may be diminished, not only by lowering the capillary pressure, but also by raising the pressure in the ureter. When the escape of urine from the ureter is prevented, the formation of urine continues until the pressure in the ureter is 40 to 50 mm. Hg below the general arterial pressure, after which no more urine is formed.

We may conclude, therefore, that the amount of urine passing through the glomeruli varies directly with the difference of pressure on the two sides of the glomerular membrane, and that it is formed by a purely physical process of filtration. An apparent exception is seen when the renal vein is ligatured: the capillary pressure rises, but the flow of urine ceases entirely.

The reason is that the flow of blood through the glomeruli ceases, and their contents soon consist of little more than a mass of blood-corpuscles, rendering filtration impossible. Test IV is successfully passed.

Glomerular filtrate though almost identical with blood-plasma minus protein is not exactly so; thus, under normal conditions

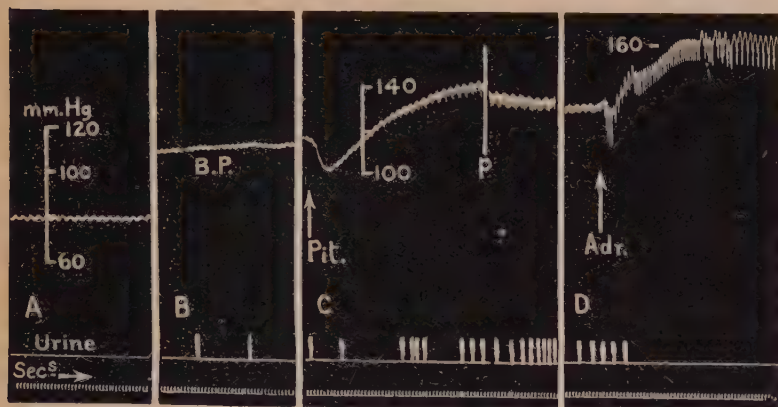


FIG. 182.—Kidney secretion of cat (urethane).

A. No secretion recorded.

B. After intravenous injection of 50 c.c. saline solution.

C. Injection of 0.2 c.c. of pituitary extract. Pause of one minute at p.

D. Injection of 2 c.c. of 1 : 10,000 adrenaline solution.

Upper tracing = carotid blood-pressure. Second line = drops of urine secreted.
Lowest line = time in seconds.

it is free from glucose because the glomerular membrane is impermeable to that sugar (when not present in excess); but if the blood becomes less alkaline or if the calcium ion content of the blood be raised, then the glomeruli become permeable to glucose (Hamburger).

Having tested the theory and found that, so far as is at present known, it fits all the facts, we must now consider in greater detail what precisely occurs in the case of the different urinary constituents. Cushney's table on p. 470 brings out the more important differences between blood-plasma and urine.

This change in composition must be effected by means of the active intervention of the cells lining the tubules, and could be brought about in one of two ways. On the one hand, the cells might secrete urea and other substances into the glomerular filtrate as this flows along the tubule; on the other hand, they might absorb water, chlorides, and glucose from this fluid. A combination of these two processes is also possible. The activity

of the cells of the tubules, whether this be secretory or absorptive, is a vital process, involving the consumption of oxygen, and the carrying out of work.

	Blood-Plasma per cent.	Urine per cent.	Change in Concentration in Kidney.
Water	90-93	95	...
Proteins, fats, and other colloids . .	7.9	nil	...
Glucose	0.1	nil	...
Urea	0.03	2.0	60
Uric acid	0.002	0.05	25
Na	0.32	0.35	1
K	0.02	0.15	7
NH ₄	0.001	0.04	40
Ca	0.008	0.015	2
Mg	0.0025	0.006	2
Cl	0.37	0.6	2
PO ₄	0.009	0.27	30
SO ₄	0.003	0.18	60

The actual work performed by the tubules can be approximately measured if the osmotic pressure of the blood-plasma and that of the urine are known. The osmotic pressure of any solution is proportional to the depression of its freezing-point (p. 70). Since the freezing-point of blood-plasma is $-0.56^{\circ}\text{C}.$, and that of urine may be as low as $-4.5^{\circ}\text{C}.$, the osmotic pressure of urine is very much greater than that of blood and the amount of work done by the kidneys in producing urine of high osmotic pressure from blood, of which the osmotic pressure is low, is extremely large.

DIURETICS.—Substances which, when they enter the blood-stream, increase the amount of urine formed by the kidneys are called *diuretics*. They fall into two groups.

Group I does not increase the oxygen consumption of the kidney. It includes sodium chloride and potassium nitrate; when hypertonic solutions of these salts are injected into the circulation they raise the osmotic pressure of the blood and bring about the condition of hydræmic plethora (p. 158). The volume of the kidney (Fig. 183) and the pressure in the glomerular capillaries are increased, and, as a result of the rise of pressure, more fluid is filtered through the walls of the glomeruli. It may be readily shown that diuretics such as sodium chloride have no specific action, but that they increase the flow of urine solely by raising the osmotic pressure. Under the influence of these diuretics, the amount of glomerular filtrate may be so large and its flow along the tubules so rapid that very little time is available for secretion or absorption on the part of the tubules, and the

urine, which is very abundant, may differ but little in composition from blood-plasma minus its protein. That the tubules take no active share in this form of diuresis is shown by the fact that the consumption of oxygen by the kidney is unaffected.

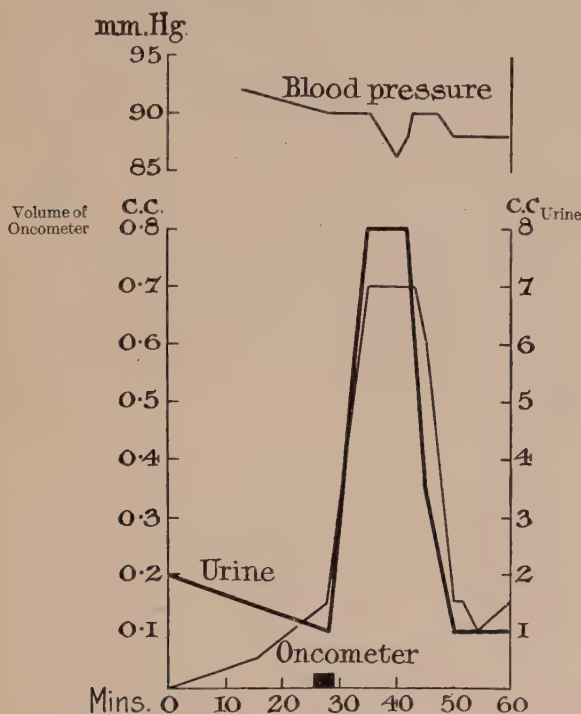


FIG. 183.—Volume of kidney, secretion of urine, and arterial pressure in a rabbit after intravenous injection of 10 c.c. of 10 per cent. sodium chloride solution. (From Cushney's *The Secretion of Urine*.)

Group II increases the oxygen consumption of the kidney. It includes sodium sulphate and urea. In mammals the injection of these substances into the blood-stream leads to an increased flow of urine containing a higher percentage of sodium sulphate or urea than is present in the blood-plasma. At the same time the kidney consumes more oxygen.

	Oxygen used by Kidney per Gramme per Minute.	Percentage of Sodium Sulphate in Urine.
(1) Normal kidney	0.04 c.c.	0.26 per cent.
(2) After the injection of sodium sulphate	0.09 c.c.	1.25 „

These results clearly point to the active intervention of the tubules as well as to increased glomerular filtration. Hence the amount of urine leaving the kidney is the resultant of the rate of filtration through the glomeruli and that of absorption by the tubules, and its composition is determined partly by these factors and partly by the composition of the blood-plasma. The fundamental difference between Cushney's and Ludwig's views is that Ludwig believed absorption to be a purely physical process, whereas Cushney regards it as being brought about by the vital activity of the tubules.

SUMMARY.—From the foregoing evidence it may be concluded that the glomeruli, in all probability, simply filter off from the blood a fluid identical in composition with blood-plasma minus its protein. The tubules absorb water, sodium chloride, and other dissolved substances from the glomerular filtrate, this process occurring to a much greater extent than has hitherto been supposed.

SECTION V

MICTURITION.—The urine formed in the kidneys passes along the ureters to the bladder, where it accumulates, the bladder being emptied from time to time by the process of micturition. The flow of urine along the ureters is assisted by rhythmic waves of contraction passing down from the pelvis of the kidney to the bladder at intervals of a few seconds; they can still be observed in the ureter when it is isolated from the central nervous system.

The wall of the bladder consists of unstriated muscular fibres arranged in three layers, an outer and an inner longitudinal layer, and a middle layer of fibres running circularly; it is lined by transitional epithelium. When the muscular walls contract they lessen the size of the cavity. The escape of urine from the relaxed bladder is prevented by two sphincters: first, circular unstriated muscular fibres forming a loop round the orifice of the bladder and called the *trigonal sphincter*, and, second, the *sphincter urogenitalis*, or compressor urethræ, which encloses the second part of the urethra, and is composed of striated muscular fibres. The bladder receives its nerve-supply from (1) the pelvic nerves, or *nervi erigentes*, stimulation of which causes it to contract, and (2) sympathetic fibres from the hypogastric plexus, stimulation of which is followed in some animals by inhibition, and in others by slight contraction, of the wall of the bladder. Afferent fibres also pass from the bladder in the pelvic nerves to the spinal cord.

Micturition is normally carried out as a reflex action which, in the adult, is controlled, and can be inhibited, by impulses from the higher parts of the brain. Distension of the bladder will give rise to impulses which, travelling to the spinal cord, reflexly bring about emptying of the bladder by the contraction of its muscular coat, the nerve-cells concerned in the reflex lying in the lumbo-sacral region of the cord ; the ready escape of urine is made possible by the simultaneous relaxation of the sphincter muscles. The intensity of the afferent impulses varies with the rate of filling of the bladder. When the bladder fills slowly, its muscular wall relaxes, and it may contain a considerable amount of urine before any appreciable tension is placed upon its muscular fibres. On the contrary, when urine is being formed rapidly, the tension within the bladder may be quickly and greatly increased by the presence of a comparatively small quantity of urine. In man, micturition usually occurs when the pressure within the bladder is about 150 mm. of water ; and if the pressure is suddenly raised to this level by injecting fluid through the urethra into the bladder, the desire for micturition is experienced.

Transection of the spinal cord in the upper lumbar region does not destroy the reflex mechanism, though it severs the path by which sensory impulses reach the brain and voluntary impulses pass to the lumbo-sacral centre. By means of voluntary impulses the emptying of the bladder can be inhibited in the adult, but in the infant such impulses are lacking and the act of micturition is purely reflex. The emptying of the bladder is usually assisted by voluntary contraction of the abdominal muscles, and in man such a contraction, by raising the intra-abdominal pressure and thereby increasing the tension within the bladder, frequently initiates the reflex action.

When the centre in the lumbo-sacral region is destroyed, for instance as the result of injury, the bladder still reacts like plain muscle elsewhere, and increased tension causes it to contract rhythmically and to expel part of its contents. As soon as the pressure within the bladder falls below a certain level, however, it fails to overcome the resistance offered by the sphincter muscles, and the bladder is not completely emptied.

CHAPTER XXII

THE DUCTLESS GLANDS

THE ductless glands comprise the suprarenal glands, the pituitary body, the thyroid and parathyroid glands, the thymus gland, the pineal gland, the spleen, and some smaller glands such as the carotid body. They are characterised by the absence of a duct. The products of their activity pass into the bloodstream, either directly or by way of the lymphatic system, and are therefore described as *internal secretions*. The spleen differs from the other ductless glands in that it is concerned with metabolic changes in the constituents of the blood rather than with the production of a true internal secretion. Its function has already been discussed (p. 68).

The formation of an internal secretion is not confined to the ductless glands. It is an important function of the pancreas, the mucous membrane of the pyloric portion of the stomach, the mucous membrane of the small intestine, the testes, the ovaries, and probably many other organs, but in the case of the ductless glands it is the only function.

The internal secretions of the ductless glands, with the exception of the spleen, belong to the class of bodies known as hormones, whose general characteristics have already been dealt with (p. 363). The presence of these hormones in the body is frequently essential to health and even to life; and the activity of the internally secreting glands is correlated with and regulates the functions of distant organs, the only link being the blood by which the hormone is carried from its place of origin to its place of action.

Much of our knowledge of the functions of the ductless glands is derived from the study of the symptoms observed in human beings in whom one or other of them is diseased. Hence it is usual in studying their functions to consider (1) the effects of disease in these glands in man, noting, on the one hand, the conditions associated with hypertrophy and presumably, increased secretion, and, on the other, those associated with atrophy, when

the secretion is diminished or absent; (2) the effect of their extirpation in animals; and (3) the effects of extracts of the glands, either upon normal animals or as therapeutic agents in man.

SECTION I

THE ADRENAL GLANDS.—Each suprarenal gland consists of an outer pale cortex partially or completely enclosing a darker central portion, the medulla.

The cortex is composed of cells arranged in radial columns and forming three zones: an outer or *zona glomerulosa*, middle or *zona fasciculata*, and inner or *zona reticularis*. The cells are polyhedral, the cell-substance being clear and often containing lipid globules. A number of arteries penetrate the capsule of the gland and open into sinusoids, which run between the columns of cortical cells towards the medulla.

The cortical sinusoids open in the medulla into venous spaces, between which the medullary cells are closely packed. These cells are granular and often pigmented; they contain a substance which stains brown with chromates, and which has therefore been described as *chromaffine* material. This is also found, apart from the suprarenal glands, in small masses of cells (paraganglia) lying along the large abdominal blood-vessels, and in or close to the sympathetic ganglia. The amount of the necessary chromaffine substance varies greatly in different groups of animals.

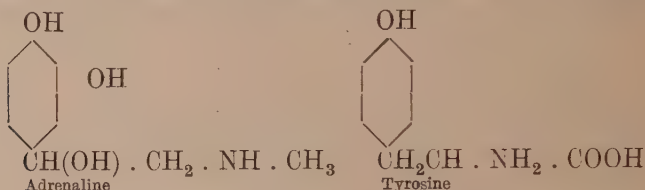
The venous spaces of the medulla open into the suprarenal vein, which leaves the gland at the hilum. The glands are supplied with splanchnic nerve-fibres from the semilunar ganglia (coeliac plexus), and a few scattered nerve-cells are present.

The cortical and medullary parts of the glands have different origins, the cortex being developed from mesodermic tissue (the Wolffian body), whereas the medulla is ectodermic, forming part of the primitive sympathetic system, from which it finally becomes separated and differentiated. In some fishes the cortical and medullary tissues persist as anatomically separate organs, and it is not known whether their coalescence into a single organ in mammals implies any physiological relationship between them.

FUNCTIONS OF CORTEX.—The cortex is essential to life. On its removal there is weakness, a fall of temperature, and death follows two or three days later. The cause is said to be defective metabolism of cholesterol. Normally the cortex is related to sex development and general growth. Cortical tumours are frequently followed by precocious sex development. Girls are stated to

menstruate at a very early age, boys to develop into the "infant Hercules" type.

FUNCTIONS OF MEDULLA.—The medulla contains a substance, *adrenaline*, which can be extracted from it in the pure condition. Structurally it is related to the amino-acid tyrosine.



Adrenaline has also been prepared synthetically.

The brown staining of the medulla, when the gland is hardened in a chromate solution, is due to the combination of the chromate with adrenaline, and the depth of the colour is roughly proportional to the amount of adrenaline present. The accessory chromaffine material, which also stains with chromate, contains adrenaline. Adrenaline is completely absent from the cortex of the suprarenal glands.

When a small amount of adrenaline is injected into the bloodstream, it produces constriction of almost all the arterioles of the body, and, if the vagus nerves have been divided, an enormous rise of blood-pressure is produced (Fig. 184). When the vagus nerves are intact the rise of blood-pressure is less (Fig. 185) because reflex slowing of the heart takes place.

The action of adrenaline is not confined, however, to the blood-vessels, but extends to every structure in the body which is normally supplied with nerve-fibres from the sympathetic system. It stimulates the nerve-endings of these fibres in the structures which they supply, and the results of the injection of adrenaline are identical with those of stimulation of the entire sympathetic system. Thus it increases the force and (if the vagi are divided) the rate of the heart, and at the same time dilates the coronary vessels, so that, in spite of the rise in arterial pressure, the efficiency of the heart is maintained and its output may even become larger. When the vagi and depressor nerves are intact, adrenaline usually causes a rise of arterial blood-pressure accompanied by a slowing of the heart (fig. 185): this is a reflex cardiac inhibition explained on p. 99 (Marey's law). It inhibits the movements of the digestive tract and (in many animals) of the bladder, but causes constriction of the ileo-colic sphincter; it may also produce sweating, erection of hairs, dilatation of the pupil, and contraction of the pregnant uterus.

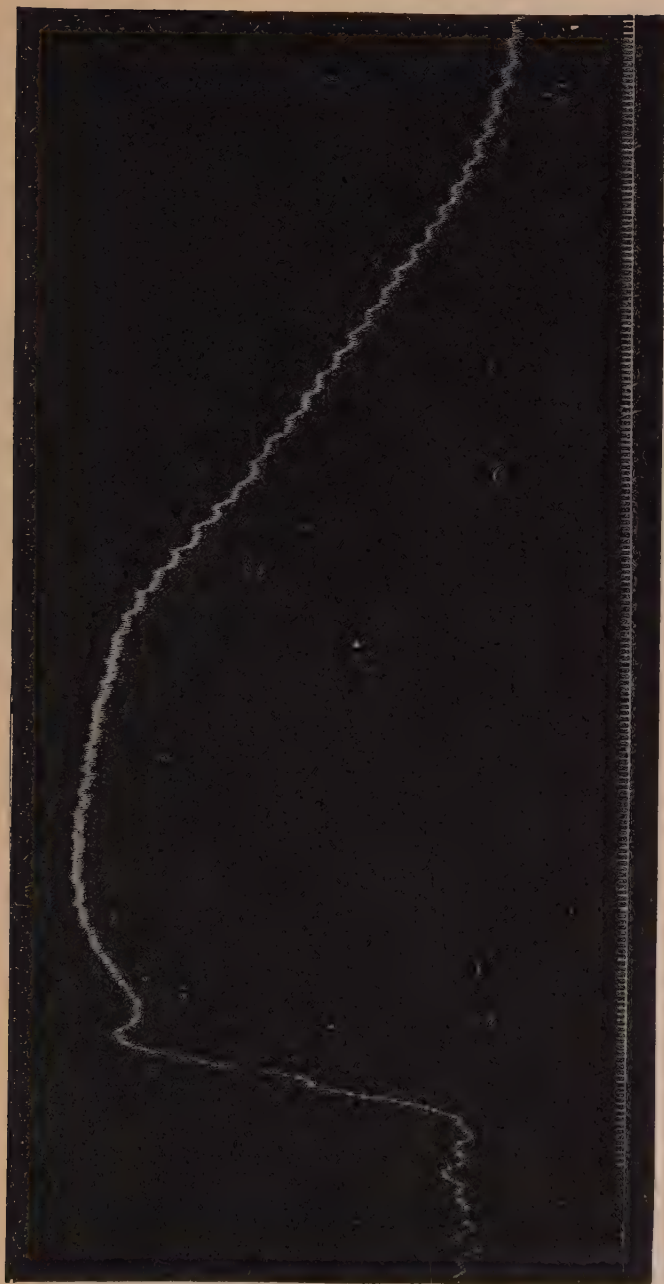


FIG. 184.—Arterial blood-pressure. Effect of injection of suprarenal extract. The vagus nerves have been divided. Time in seconds. (From *Practical Physiology*, by Pembrey and others.)

Respiration is temporarily suspended by an injection of adrenaline, owing, it is stated, to sudden anæmia of the respiratory centre. It causes dilatation of the bronchiole muscles. For this reason it is a valuable drug in cases of asthma.

ADDISON'S DISEASE.—We must now correlate what has been said above as to the functions of cortex and medulla with the symptoms which accompany diseases of the adrenals. The symptoms described by Addison in 1855 are prostration, vomiting,

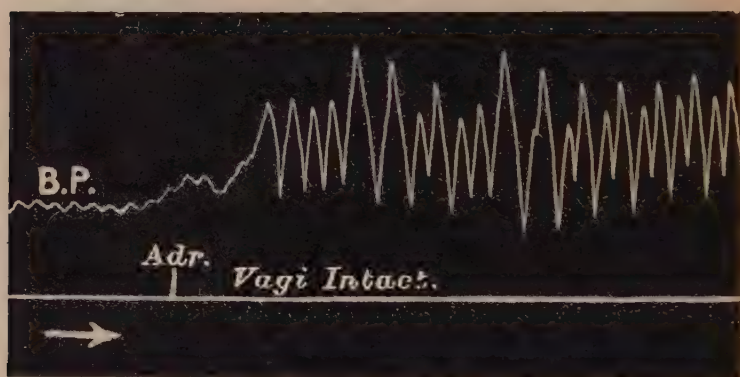


FIG. 185.—Tracing of arterial pressure. Effect of injecting 0.05 mg. of adrenaline into a vein.

Note the marked slowing of the heart.

muscle wasting, and pigmentation of the skin. The blood-pressure is very low and this may explain the prostration. The bronzing of the skin is probably due to the production of melanin by the action of a ferment on the tyrosine which accumulates since the glands do not use it up for the formation of adrenaline. The other symptoms are very likely due to the disturbance of the cortical function.

THE POINT OF ACTION OF ADRENALINE.—This is not on the sympathetic endings proper, but probably on some receptor substance (neuro-muscular junction) which lies between the actual nerve-ending and the muscular fibre, and does not degenerate when the post-ganglionic fibres are divided. Proof is afforded by the following experiment. When the cervical sympathetic nerve, which supplies the iris, is stimulated, or when adrenaline is injected into a vein, the pupil dilates. If the superior cervical ganglion on one side is removed, the post-ganglionic fibres and their nerve-endings degenerate, and, when time has been

allowed for their degeneration, electrical stimulation of these fibres produces no effect on the pupil, whereas on the injection of adrenaline the pupil dilates much more fully than in the normal animal.

SECRETION OF ADRENALINE.—Adrenaline is constantly being formed by the suprarenal glands, from which it passes into the blood-stream, and it is thus a true internal secretion. This secretion can be increased in amount by stimulation of the splanchnic nerves, which contain secretory fibres for the suprarenal glands. The nerves may be stimulated either directly, *e.g.* by stimulation of the peripheral end of a divided splanchnic nerve, or reflexly, the centre for this reflex being very near the vaso-motor centre. The occurrence of reflex secretion of adrenaline by the suprarenal glands can be demonstrated in the following manner: one splanchnic nerve, *e.g.* the left, is divided in the cat, so as to cut off the efferent path to that gland; and it is found that, as the result either (1) of stimulation of sensory nerves, or (2) of violent emotion, such as pain or fear, the adrenaline is discharged more or less completely from the right suprarenal gland, while the left gland remains unaffected. Evidently division of a splanchnic nerve, by breaking the efferent side of the reflex arc, prevents any reflex secretion of adrenaline from the corresponding gland into the blood-stream. The effects of stimulation of the splanchnic nerve, and the consequent setting free of adrenaline, on the arterial blood-pressure and on the constriction of arterioles outside the splanchnic area, have already been described (p. 146). Anæsthetics, such as chloroform, also excite the centre and bring about a discharge of adrenaline.

In all probability the varying activity of the suprarenal glands, brought about by impulses reaching them along the splanchnic nerves, plays an important part in the adjustment of the vascular system to the changes constantly taking place in the body. A striking instance of this adjustment is seen in states of violent emotion, such as rage, pain, or fear. The additional adrenaline sent into the blood-stream, in these circumstances, increases the amount of glucose passing from the liver into the blood, thereby providing a further supply of sugar to the skeletal muscles; and, in so far as it raises the blood-pressure, it also improves the nutrition and efficiency of the heart and the blood-supply to the brain. In this way the reaction of the animal to these emotional states, by movements of attack or defence, is rendered more effective.

Owing to its action on the blood-vessels, adrenaline has proved of great value in checking hæmorrhage when applied locally.

SECTION II

THE PITUITARY BODY (HYPOPHYSIS CEREBRI).—The pituitary body lies in the sella turcica, and is connected with the floor of the third ventricle by a hollow stalk. It consists of two lobes, differing from each other both in origin and appearance (Fig. 186). The anterior portion is formed from a hollow upgrowth of buccal ectoderm, the posterior part from a hollow

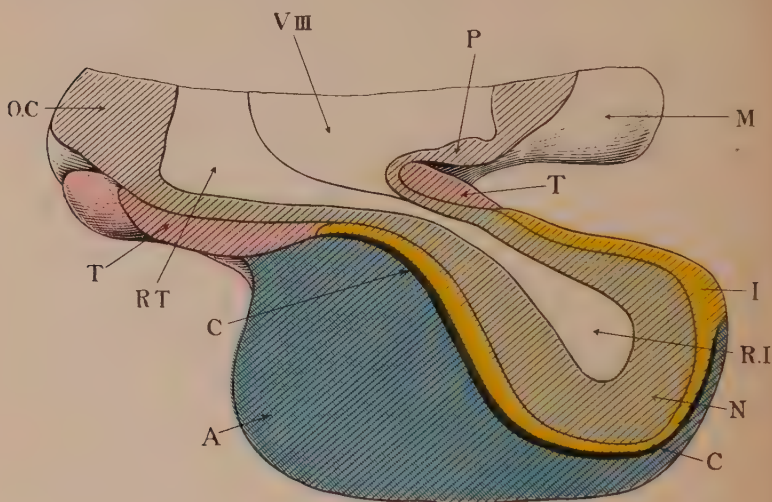


Fig. 186.—Section through pituitary gland of cat.

O.C, optic commissure.

T, pars tuberalis.

RT, recessus tuberalis.

C, cleft between pars anterior and pars intermedia.

A, pars anterior.

N, pars nervosa.

R.I, recessus infundibuli.

I, pars intermedia.

M, corpora mammillaria.

P, praemammillary area.

VIII, third ventricle.

downgrowth from the floor of the third ventricle. Between lies the pars intermedia. The cavity of the ectodermic portion persists as a cleft, separating the anterior and posterior lobes of the fully developed hypophysis. The cavity of the nervous portion becomes obliterated in man, except in the stalk. The anterior lobe, or *pars anterior*, is glandular in structure. The posterior lobe consists of two parts: (1) the *pars nervosa*, composed of neuroglia, and (2) the *pars intermedia*, a thin layer, ectodermic in origin, applied to and partially surrounding the anterior portion of the pars nervosa. In addition to the anterior, intermediate and posterior parts there is the *pars tuberalis*. (See Fig. 186.)

STRUCTURE OF THE PARS ANTERIOR.—The pars anterior consists of columns and groups of cells, and has a rich blood-supply. The cells are of two kinds, clear and granular; most of the granular cells contain eosinophile granules, but some contain basiphile granules. The pars intermedia also consists of columns of cells, but these contain finer granules than the granular cells of the pars anterior, and some show a hyaline or colloid change. Colloid material is also present between the cells, and the same substance is found in spaces in the pars nervosa, and may sometimes be traced into the cavity of the infundibulum. The colloid of the hypophysis differs from that of the thyroid gland in containing no iodine.

FUNCTIONS OF THE PARS ANTERIOR.—Removal of the greater part of the pituitary body in young animals leads to retardation of growth, to failure of sexual development, and to obesity (Fig. 187). Similar results follow accidental injury in



FIG. 187.—On the left a dog twelve months old: its pituitary body was partially removed at the age of eight weeks. On the right a normal dog of the same litter. (Aschner.) (From Schafer's *The Endocrine Organs*.)

children, but, in contrast with the effects of thyroid deficiency, mental development is not seriously impaired; when it occurs in the human subject, the condition is known as *infantilism*.

Hypertrophy of the anterior lobe of the gland in man produces the disease known as *acromegaly*; the chief features of this disease are enlargement of the bones, especially those of the hands, feet, and face (Fig. 188), thickening of the skin, increased sexual activity, and frequently glycosuria. If the enlargement

of the pituitary body occurs in early life, before the epiphyses have united with the long bones, these bones increase greatly in length and the subject becomes abnormally tall, the condition being known as *gigantism*.

Atrophy of the anterior lobe leads to adiposity, stunted skeletal growth, lower metabolism than normal, mental backwardness, decreased sexual activity; sugar tolerance is usually high.

Both the experimental and clinical evidence make it clear that the anterior lobe produces and sends into the blood-stream



FIG. 188.—Four photographs of the same person showing the gradual development of acromegaly. A, at twenty-four years of age (normal); B, at twenty-nine (onset of disease); C, at thirty-seven; D, at forty-two. (Cushing.) (From Schafer's *The Endocrine Organs*.)

one or more substances, presumably hormones, which influence growth and sexual development. It might be expected, therefore, that the administration of the anterior lobe, or of extracts of it, to young growing animals would stimulate their growth, and would cause them to attain a larger size than normal animals. Such is the case. Huge rats have been produced by injecting the extract of the pars anterior into the peritoneal cavities.

STRUCTURE OF THE PARS POSTERIOR.—The pars posterior consists of two parts, the pars nervosa and the pars intermedia. The pars nervosa is highly vascular. The cells are neuroglial in type. They form rough tubes containing a colloid material which is thought to originate in the pars intermedia and to be passing on into the third ventricle. The pars intermedia consists of masses of basophil cells which form sinuses. These are filled with the same colloid material as that contained in the pars nervosa.

FUNCTIONS OF THE PARS POSTERIOR.—The functions of the pars posterior are to secrete "pituitrin." This contains two active principles, oxytocin and vaso-pressin.

Oxytocin stimulates the uterus to contract. In animals a virgin uterus will do this. In women the uterus must be "in labour." This property is very valuable in child-birth.

Vaso-pressin causes arterioles and capillaries to contract. It is very valuable in shock.

Owing to the constriction, there is a considerable rise of arterial blood-pressure, and since the renal vessels are not constricted a result of the injection is the increased flow of urine, due to the increased flow of blood through the kidney.

Other plain muscles such as the bladder, bronchiole muscles and intestine are sent into vigorous contraction by the injection. The same effect is produced on the plain muscle in the wall of the milk sinuses of the lactating mammary gland, so that there is an increase in the amount of milk escaping from the gland. But the total yield of milk in the course of twenty-four hours is not increased beyond the normal by the administration of pituitary extract. The extract does not increase the formation of milk, but merely causes contraction of the unstriated muscle in the ducts and alveoli, so that the gland is more completely emptied than would otherwise be the case.

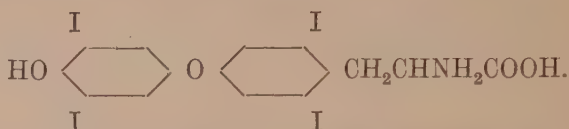
The action of vaso-pressin on plain muscle differs in several respects from that of adrenaline. First, the former acts directly on the muscle, whereas adrenaline stimulates the sympathetic nerve-endings; second, vaso-pressin leads to contraction of all unstriated muscle, in contrast with adrenaline, which inhibits some muscle—for example, that of the digestive tract; and, third, vaso-pressin extract is more prolonged in its effects than that of adrenaline.

SECTION III

THE THYROID GLAND.—This is composed of closed spherical vesicles of varying size, held together by connective tissue. Each vesicle contains a viscid, colloid material surrounded by a single layer of cubical cells, with no basement-membrane. The thyroid gland contains iodine in organic combination, in a compound which has been named *thyroxine*. In this compound, the constitution of which is now known, the iodine is combined with a substance resembling tyrosine. The thyroid probably produces about 1 mg. of thyroxine per day.

The gland is richly supplied with blood-vessels and nerves. Numerous lymphatic vessels are also found in it, and these may sometimes be seen to contain colloid material.

THYROXINE is chemically related to tyrosine. Its structural formula is



It has a most marked effect on the rate of metabolism. It may be given by the mouth. One milligramme injected into the body causes the oxidation of about 250 grammes of glucose with the liberation of over 1000 calories of heat. The temperature is thus raised. The heart beats more rapidly. The blood-pressure rises. The blood-flow through the heart per minute is increased. The respirations are more frequent. The skin is moist. The appetite is excellent. Fat-depôts tend to be depleted.

HYPOTHYROIDISM.—Attention was first called to the importance of the thyroid gland by the observation that it is atrophied in the disease known as *myxœdema* (Fig. 189). The



A

B

FIG. 189.—Case of myxœdema (A) before and (B) after treatment.
(By permission of the Editor of *The Practitioner*.)

symptoms of myxœdema are obesity, dryness and thickening of the skin, falling out of the hair, slowness of mental processes and of speech ; indeed, all the metabolic processes in the body become more sluggish, and the respiratory exchange is diminished.

The effect of operative removal of the thyroid in man, or experimental removal in animals, may be complicated by the results of simultaneous removal of the parathyroid glands, which, especially in carnivora, are often imbedded in the substance of the thyroid. When the latter is removed without interference with the parathyroids, typical myxœdema develops. This is especially well marked in monkeys. The myxœdema produced in this way can also be cured by feeding with thyroid gland substance or an extract of it.

Deficiency of the gland at birth gives rise to the condition known as *cretinism*, in which growth, both physical and mental, is extremely retarded; a cretin aged fifteen to eighteen years may resemble a child of two or three years of age in its size and mental development. The symptoms, both of cretinism and of myxœdema, are due to the absence of some substance normally formed by the thyroid gland, from which it passes into the lymphatics and thence into the blood-stream. This is shown by the fact that extracts of the gland, or the gland itself, when given by the mouth, lead to complete recovery in myxœdema and to very marked improvement in cretinism.

HYPERTHYROIDISM.—In the disease known as *exophthalmic goitre* the thyroid is enlarged, and the symptoms are in marked contrast with those of myxœdema. The patient loses flesh, there is great nervous excitability, an increased pulse-rate, and protrusion of the eyeballs (Fig. 190). Associated with the loss of flesh there is increased metabolism, with a corresponding increase of the output of nitrogen and carbon dioxide, and an increase of oxygen usage (basal metabolism) often by more than 50 per cent. above the normal level. The vesicles of the thyroid gland show evidence of activity in the fact that the epithelial cells assume a more columnar shape, and the contents are more fluid than is normally the case.

The profound influence of the thyroid on normal develop-



FIG. 190. Case of exophthalmic goitre.
(From Schafer's *The Endocrine Organs*.)

ment is well shown by experiments on tadpoles. If the thyroid is removed from a tadpole, metamorphosis is inhibited ; on feeding with fresh thyroid it recommences. Conversely, if a tadpole is fed with thyroid, its metamorphosis is greatly accelerated and outstrips its growth, so that a minute frog results, much before its proper time.

SECTION IV

THE PARATHYROID GLANDS.—The parathyroid glands are four in number, two on each side, and lie close to, or imbedded in, the thyroid gland. They are quite small, and each is composed of a mass of cells, sometimes arranged in columns. Many of the cells have clear cytoplasm, and some of these may contain glycogen. Others are characterised by containing eosinophile granules. Our knowledge of the function of the parathyroids is derived almost entirely from observations on the effects of their removal in animals or in man. Extirpation of all four glands is followed in a day or two by acute symptoms, which are, for the most part, of nervous origin. The excitability of the central nervous system is increased, and reflexes are not only evoked more readily, but are unusually vigorous ; tremors of the skeletal muscles, and from time to time prolonged muscular spasm and even convulsions, also occur. Since the muscular twitchings and the convulsions cease after section of the motor nerves, they must be central in origin ; and it is probable that they result from abnormal excitability of the spinal motor neurones. The condition is known as *tetany*, and, although recovery frequently occurs, it is sometimes fatal in a few days, more especially in carnivora and in young animals. There is some evidence that vaso-motor reflexes are evoked more readily after parathyroidectomy, and that the irritability of the sympathetic system is also exaggerated. The blood calcium is found to fall in tetany. The administration of calcium salts by the mouth or by venous injections temporarily cures the condition. A more lasting cure is obtained if in addition the parathyroid hormone (Collip) is administered intravenously. Vitamin D might also be given with advantage.

Noel Paton has shown that the injection of guanidine is followed by symptoms which closely resemble those of parathyroid tetany. It is probable that this substance has no connection with tetany because the administration of the parathyroid hormone which cures tetany does not cure the guanidine tetany.

SECTION V

THE THYMUS.—The thymus is composed of lobules united by connective tissue ; each lobule consists of an outer denser cortex and an inner medullary part, the cortex being subdivided by strands of connective tissue into a number of compartments. Both the cortex and medulla are composed of a meshwork of fibrils covered with flattened cells, the meshes being occupied by lymphocytes. In the medulla are found a number of small masses of flattened epithelial cells arranged concentrically ; they are called Hassal's corpuscles. The gland is abundantly supplied with blood-vessels. In man it reaches its maximum size during the first two or three years of life, and then becomes smaller, usually disappearing with the occurrence of puberty, and being almost completely absent in the adult. After its removal in animals, the testes develop more rapidly, and, conversely, castration delays the atrophy of the thymus. When young animals receive fresh thymus with their food, sexual maturity is delayed, and, in the male, degeneration of the testis takes place.

By feeding tadpoles with thymus tissue, growth is accelerated, but metamorphosis retarded.

The thymus thus appears to exercise a restraining influence on post-natal development, *e.g.* of the reproductive organs, and to undergo atrophy when its function has been accomplished. In rabbits the atrophy occurs at an earlier date if the animals are utilised for breeding purposes.

The thymus is found enlarged in status lymphaticus.

CHAPTER XXIII

REPRODUCTION

SECTION I

IN the higher forms of life, the continuance of the species is effected by means of certain tissues set apart for this purpose. These form cells which develop into a new animal of the same species, the process constituting reproduction. In most animals these cells are of two kinds, namely, spermatozoa and ova, formed by the reproductive organs of the male and female respectively ; a spermatozoon and ovum fuse to form a new cell which develops into an animal resembling its parents in its general character. This, again, is capable of reproducing itself.

CELL DIVISION (MITOSIS).—When a cell divides in the somatic tissues, the process is initiated by changes in the centrosome and nucleus, which constitute the process of *karyokinesis* or *karyomitosis* (Fig. 191). The centrosome usually lies near the nucleus, and is surrounded by astral rays. Together these form an attraction sphere. When a cell is about to divide, the attraction sphere divides into two. These pass towards opposite poles of the nucleus, but remain connected by a spindle of fine threads, the *achromatic spindle*. Meanwhile the chromatin of the nucleus becomes arranged in the form of a continuous skein, which is then broken into short lengths, the *chromosomes*. The number of chromosomes is constant for any one animal species, and in man there are forty-eight. The chromosomes are arranged around the equator of the achromatic spindle, each being V-shaped, with the apex of the V pointing towards the centre. This forms the monaster. Now each chromosome splits longitudinally to form two, one of which passes to each pole of the achromatic spindle. The result of this is the formation of the diaster. The further change consists in the formation of a daughter-nucleus by a reversal of the processes which occurred in the anaphase ; that is, the chromosomes unite to form a skein, which then becomes transformed into the ordinary nucleus.

At the same time constriction of the protoplasm of the cell is taking place in the neighbourhood of the equator of the achromatic spindle, the spindle itself disappears, and finally each

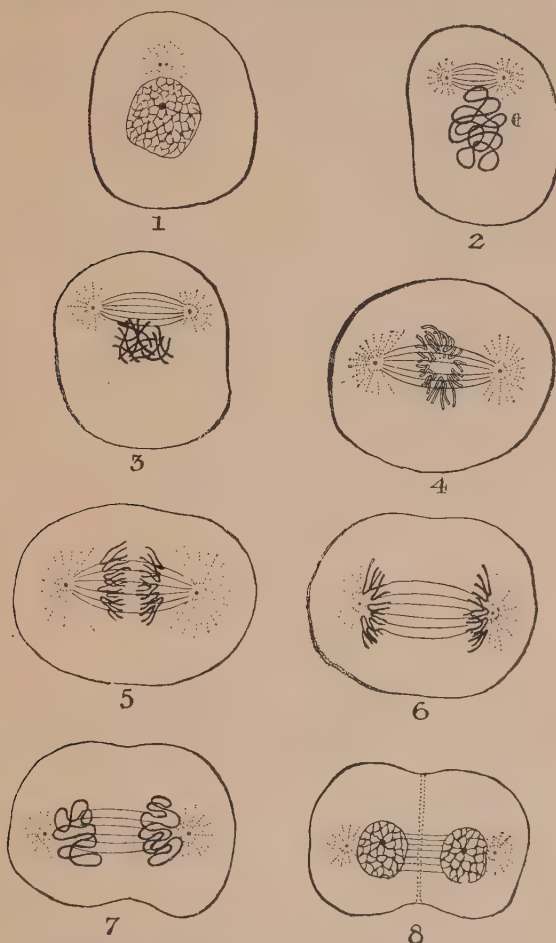


FIG. 191.—Karyokinesis. (From Gray's *Anatomy*.)

1 to 4, Anaphase; 5, 6, Metaphase; 7, 8, Kataphase.

daughter-cell assumes a separate existence. The process of nuclear division has been observed in living cells in tissue cultures and occupies from thirty minutes to three hours.

MATURATION OF GERM-CELLS.—In the germ-cells the mitotic process is somewhat different. Each cell divides twice, the first division being by *heterotypical mitosis*, in which each

two of the original chromosomes become united by their free ends to form a ring. This breaks across, so that each daughter-nucleus possesses half the number of chromosomes found in the parent-cell. In the second division each chromosome splits longitudinally in the ordinary way (*homotypical mitosis*). In the spermatocytes this process results in the formation of four spermatids, equal in size, each of which becomes a spermatozoon

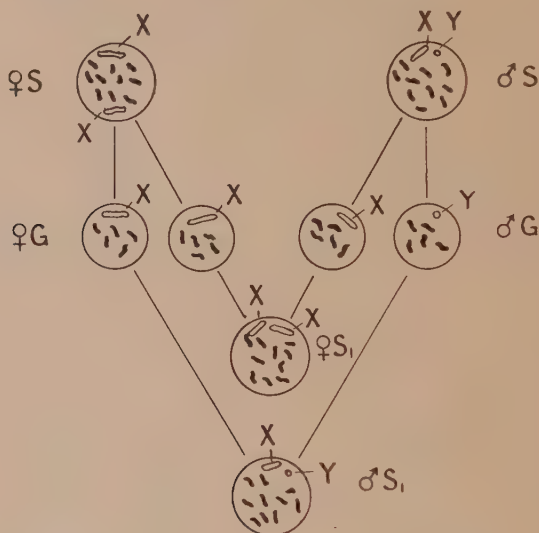


FIG. 192.—Diagram to illustrate principle of sex-determination in an animal with 12 chromosomes in the somatic cells. ♀S, female somatic cells with two X-chromosomes; ♂S, male somatic cells with one X- and one Y-chromosome; ♀G, ripe ova each with one X-chromosome; ♂G, the two types of ripe spermatozoa, one with an X-, the other with a Y-chromosome; ♀S₁, fertilised ovum to form female; ♂S₁, fertilised ovum to form male.

and contains half the number of chromosomes peculiar to the species of animal. In the ovum the first division, which takes place after discharge from the ovary, is into a large and a small cell (the first polar body). The large cell again divides into two cells of unequal size, the larger of the two being the mature ovum, and the smaller the second polar body. The first polar body may or may not divide into two small cells. If it does so, the two stages of subdivision result in the formation of four cells, each containing half the number of chromosomes peculiar to the species of animal, but only one of these becomes a mature ovum, and the other three undergo atrophy.

FERTILISATION takes place as a result of the introduction of spermatozoa into the vagina during the act of coitus. The motile spermatozoa travel into the uterus and Fallopian tubes, where they may live for some days. If a spermatozoon penetrates into an ovum, the spermatozoon loses its tail, changes take place in its head and neck, and it is converted into a male pronucleus, which fuses with the nucleus of the ovum (female pronucleus) to form a new cell containing the normal number of chromosomes; this process constitutes fertilisation.

SEX-DETERMINATION.—The somatic cells of females have two of their chromosomes slightly different from the rest, and are called the sex (or X) chromosomes. In the maturation of the germ cells one X-chromosome remains in each ripe ovum. The male somatic cells contain sex-chromosomes of two types, one called X and one called Y, and on maturation one passes to each ripe spermatozoon. There are thus two kinds of spermatozoa, one containing one X-chromosome, the other containing one Y-chromosome. The remaining chromosomes are of the usual type. When an X-spermatozoon fertilises an ovum, a 2X cell results, and the offspring is a female; when a Y-spermatozoon fertilises, the fertilised cell is an XY cell and the offspring is male. (Fig. 192.)

SECTION II

THE MALE REPRODUCTIVE ORGANS.—These consist of the testes, which form spermatozoa, and of accessory organs, namely, the vesiculæ seminales, the prostate gland, the glands of Cowper, and the penis.

Each testis is covered by a strong fibrous capsule, the *tunica albuginea*, from which trabeculae pass into the gland, dividing it into lobules, which contain the seminal tubules. Each tubule is convoluted, and consists of a lining epithelium several layers thick, resting upon a laminated basement-membrane. The cells nearest the basement-membrane are called *spermatogonia*; these divide, giving rise to the *spermatocytes*, which lie more internally. Within the layer of spermatocytes, and formed from them by division, are the *spermatids*, which develop into *spermatozoa*. Lying in the connective tissue between the tubules are groups of polyhedral cells, called *interstitial cells*. The seminal tubules lead into straight tubules (*rete testis*) which open into the *epididymis*; this is a convoluted tube lined by ciliated cells, and is continued as the *vas deferens*, a tube with a thick muscular wall, which opens into the prostatic part of the

urethra. The vesiculæ seminales are branched sacculated outgrowths from the vas deferens. The *prostate gland* surrounds the first part of the urethra, and is made up of numerous branched, glandular tubes supported by connective tissue and unstriated muscular tissue. It forms a secretion which has the property of stimulating the spermatozoa to active movements, though at the same time shortening their lives.

The *penis* consists of erectile tissue, which forms the corpus spongiosum and the two corpora cavernosa, and it contains the urethra; the erectile tissue is made up of a meshwork of elastic and muscular tissue; arterioles open directly into the spaces in the meshwork, the blood escaping into veins. When the muscular fibres of the arterioles are relaxed, and the veins are compressed by the bulbo-cavernosus muscle, the spaces become distended with blood, causing erection of the organ.

The formation of spermatozoa begins at puberty, and each spermatozoon consists of a head, body, and tail, and is actively motile. The fully formed spermatozoa pass from the testis into the epididymis and vas deferens, and so to the urethra.

THE INTERNAL SECRETION OF THE TESTES.—Experiment shows the importance of the internal secretion of the testis. If the testes are removed before puberty, hair does not grow on the face, the voice does not break, there is mental depression, the skeletal growth is abnormal, the adipose depôts are hypertrophied, sex feeling is lost. If removed after puberty the mental depression is the most marked symptom; sex feeling is usually lost. Tying the vas deferens is said to cause degeneration of the seminiferous tubules. But this is accompanied by proliferation of the interstitial cells, the result being an increase in the general bodily vitality. Grafting of adult testes in the tunicæ albuginæ of the senile has also been claimed to prolong youth.

SECTION III

THE FEMALE REPRODUCTIVE ORGANS.—The female generative organs are the ovaries, Fallopian (uterine) tubes, uterus, and vagina.

The ovary is a solid organ composed of fibrous tissue (stroma), with many spindle-shaped cells, and is covered by a layer of cubical cells called the germinal epithelium. Groups of *interstitial cells* are found in the stroma, similar to those which occur in the testis. The ovary contains many vesicles of varying size (Graafian follicles), and a large number of primordial follicles;

the latter are formed during foetal life from down-growths of the germinal epithelium into the stroma, and each consists of an ovum surrounded by a layer of flattened cells.

The *ovum* is a large spherical cell enclosed in a striated envelope called the *zona pellucida* (striata); its protoplasm, which is abundant, is filled with fatty and albuminous granules, and contains a spherical nucleus (germinal vesicle) with a nucleolus.

THE GRAAFIAN FOLLICLE.—At puberty some of the primordial follicles develop into Graafian follicles (vesicular ovarian follicles). The epithelial cells covering the ovum multiply to form a mass in which fluid appears, separating the epithelium into two parts: an outer layer, the *membrana granulosa*, forming the wall of the follicle, and an inner layer, the *discus proligerus*, surrounding the ovum. At this stage the whole follicle is enclosed in a fibrous capsule derived from the stroma. As the amount of fluid increases, the follicle approaches the surface of the ovary, and eventually bursts, the ovum being set free and passing into the Fallopian tube. The process just described is called *ovulation*. The space left by the escape of the ovum and fluid is filled up by the ingrowth of vascular processes from the surrounding tissue, forming the *corpus luteum*, so called because its cells are yellowish in colour owing to the presence of a fatty pigment, *carotene* (or *lutein*). The corpus luteum gradually undergoes fibrous changes and disappears within two months. If pregnancy occurs, it becomes much larger and does not disappear until after parturition. The primordial ova are extremely numerous in the ovary, but only a small proportion of them develop into Graafian follicles, and only a few of the latter reach maturity, the others, after developing to a certain extent, undergoing atrophy. During sexual life ovulation usually occurs once a month, a single ovum being discharged on each occasion. The process is intimately bound up with menstruation.

THE UTERUS.—The uterus consists of two parts, the body and the cervix. Its cavity is lined by a thick mucous membrane, composed of soft connective tissue covered by ciliated epithelium which dips down into the membrane to form long tubular glands.

The mucous membrane rests on a thick muscular coat, composed of unstriped muscle, and arranged in three layers. The outer (subserous) layer is comparatively thin, and the fibres are arranged in sheets arching over the fundus. The middle (vascular) layer is thick; the fibres are arranged partly in sheets arching over the fundus, and partly in concentric rings round

the larger blood-vessels. In the inner (submucous) layer, the muscular fibres form concentric rings round the body of the uterus.

The uterus receives its nerve-supply solely from the sympathetic system. The nerve-fibres leave the spinal cord in the anterior roots of the second of the fifth lumbar nerves, and reach the uterus by way of the inferior mesenteric ganglia and the hypogastric nerves. In the case of the human uterus, impulses passing along these nerves to the uterus always bring about contraction of the uterine muscle, whether the uterus is pregnant or non-pregnant.

The *Fallopian (uterine) tube* consists of a mucous membrane thrown into numerous longitudinal folds and lined by ciliated epithelium. The mucous membrane rests upon a muscular coat, consisting of smooth muscles, the outer fibres being longitudinal and the inner circular.

Both the uterus and Fallopian tubes are covered by a serous membrane derived from the peritoneum.

MENSTRUATION.—This marks the onset of puberty, and the first menstrual period usually occurs between the ages of 13 and 16 ; as a rule, it recurs once a month until about the age of 45, its cessation at this age being called the *menopause*.

During each menstrual cycle the mucous membrane of the uterus undergoes a series of changes which as usually described take place in four stages. (1) A few days before the onset of menstruation the mucous membrane of the uterus becomes congested and thickened. (2) During the menstrual period some of the blood-vessels of the mucous membrane rupture ; the escaping blood, together with the superficial epithelium of the uterus and the secretion of the uterine glands, forms the menstrual flow, which lasts four or five days, the loss of blood varying from 100 to 200 c.c. (3) At the conclusion of the menstrual period the uterine mucous membrane is gradually regenerated. This stage is succeeded by (4) a resting period lasting for some days and passing into the stage of congestion which initiates the next menstrual cycle.

Menstruation is associated with feelings of malaise and often with a slight rise of body-temperature. It is absent during pregnancy, and usually during lactation, and is normally associated with, though not dependent upon, ovulation. Menstruation ceases after the removal of the ovaries, and also at the menopause, when ovulation no longer takes place. Its object appears to be to render the condition of the uterus, at the end of the menstrual period, suitable for the reception and development of the ovum if fertilisation takes place. In many of the lower animals a

somewhat similar change in the uterus, known as the *œstrus*, occurs at certain seasons of the year, and is accompanied by ovulation and sexual activity.

The close association between ovulation and menstruation has led to the view that the corpus luteum, formed each month as a sequel to ovulation, produces a hormone which brings about the uterine changes culminating in menstruation. Parkes and his co-workers have extracted from ovarian tissue a substance, "œstrin," which causes menstruation when injected into the blood.

SECTION IV

DEVELOPMENT.—After fertilisation the ovum at once divides. If it has been fertilised in the Fallopian tube, it has already divided and subdivided to form a small mass of cells called a *morula* by the time it enters the uterus.

The further development of the morula takes place in the uterus and constitutes *pregnancy*. The morula becomes imbedded in the uterine mucous membrane, which then consists of three parts: namely, (1) the *decidua basalis*, lying between the embryo and the muscular wall of the uterus; (2) the *decidua capsularis (reflexa)*, between the embryo and the cavity of the uterus; and (3) the *decidua vera*, lining the remainder of the uterus. As the embryo grows, it becomes enclosed in a sac filled with fluid and called the amnion; surrounding the amnion is a vascular membrane, the chorion, from which blood-vessels pass in the umbilical cord to and from the foetus. After the third month of pregnancy the foetus receives its nutrition from the *placenta*, which is formed partly from maternal and partly from foetal (chorionic) tissue. It consists essentially of large blood-spaces in the *decidua basalis*, into which open the uterine arteries, and from which the blood of the mother is carried into the uterine veins. Projections from the chorion (chorionic villi), containing foetal blood-vessels, lie in these spaces and are bathed by the maternal blood; the blood reaches the villi along the umbilical arteries, and is returned to the foetus in the umbilical vein. The maternal and foetal blood are thus separated by a double layer of epithelium, and the nutrition of the foetus is effected by the diffusion of oxygen and nutritive material through this epithelium.

PARTURITION.—The average duration of pregnancy is 280 days, during which the muscular wall of the uterus not only increases in size, but becomes greatly thickened. Parturition is brought about by rhythmic contraction of the uterine muscle, and

the foetal membranes and their contained fluid are forced through the os uteri, which becomes fully distended. This, the first, stage of labour ends when the os uteri is fully dilated; and the membranes rupture about this time.

The foetal head then enters the pelvis, and the uterine contractions become more prolonged and frequent, being accompanied by voluntary contraction of the abdominal muscles. The foetus is gradually forced through the pelvic canal and vulva, the head normally being born first. The second stage of labour ends when the child is born. The whole process of parturition varies greatly in duration, and may last twenty-four hours. Shortly after the birth of the child the uterus contracts further and expels the placenta. This is a large disc-shaped structure, one surface of which is smooth owing to the presence of a covering of amniotic membrane. The umbilical vessels enter the placenta at the middle of the smooth surface.

After parturition the uterus rapidly decreases in size, this being known as *involution*.

THE MAMMARY GLAND.—The mammary gland consists of a number of lobules imbedded in fat and areolar tissue. Each lobule is composed of alveoli, lined by cubical or columnar epithelium resting on a basement-membrane. The ducts open on to the nipple, and are lined by cubical epithelium; their walls contain unstriated muscular fibres. Near the nipple each duct dilates to form an ampulla.

THE SECRETION OF MILK.—When pregnancy occurs, it is associated with an increase in size of the mammary gland, due to growth of glandular tissue and increase in size and vascularity of the alveolar cells. The glandular development is brought about by a hormone formed in the corpus luteum. This is indicated by the observation that, if a Graafian follicle is artificially ruptured in a non-pregnant animal, a corpus luteum is formed and the mammary glands develop for a short time. Further, it has been shown that the repeated injection of an extract of corpus luteum into a virgin rabbit leads to growth of the mammary glands. That their development is due to chemical, and not to nervous, influences is also indicated by the fact that, even after the severance of all nerves to a mammary gland, the gland undergoes normal development during pregnancy.

Towards the end of pregnancy the mammary glands become filled with a protein-containing fluid, colostrum. This increases in amount when birth takes place and is available for the nourishment of the infant during its first two or three days of extra-

uterine life. If colostrum is deficient in amount the infant may with advantage be given, by means of a bottle, tap water which has been boiled and allowed to cool to 37° C.

The *secretion* of milk (lactation) begins two or three days after the birth of the infant, and normally continues for six to nine months or even longer. The exciting cause of the onset of secretion appears to be somewhat complex. It is not nervous, for secretion can occur after division of all the nerves to the mammary gland. It must therefore be chemical, and more than one hormone appears to be concerned in lactation. With the atrophy of the corpus luteum which takes place at this time, the anabolic stimulus is withdrawn, and katabolism tends to occur. There is evidence that the foetus itself furnishes a hormone which inhibits the production of milk, and after parturition this inhibitory influence is necessarily removed.

The continuation of lactation is dependent upon the suckling of the infant. In the absence of suckling, secretion ceases, and the glands diminish in size. This fact suggests that lactation may be reflex in origin, and there is no doubt that it is influenced by emotional states. The experimental evidence that the secretion may occur when all nerves to the gland have been divided, however, shows that it cannot be purely nervous in origin; and it is possible that the act of suckling may influence the secretory mechanism directly, probably mechanically.

The rate of milk secretion appears to be determined by the rate of blood-flow through the mammary gland, and the effect of manipulation in promoting secretion is probably due to the increased blood-supply which results.

The characteristic constituents of milk—lactose, caseinogen, and fat—are not directly abstracted from the blood, but are synthesised in the mammary gland from precursors present in the circulating blood. The lactose is formed from blood glucose, the caseinogen synthesised from amino-acids, and the fat and phosphates from the phosphatides of the blood.

Histological changes take place in the alveolar epithelium during lactation, and these do not occur uniformly throughout the gland. In a section, one group of alveoli may show active production of milk, while another group exhibits a resting stage. The active cells are columnar in shape, and contain globules of fat; these are larger towards the lumen of an alveolus, into which the ends of the cells project, and sooner or later become broken off. In the resting stage of the alveoli the lining epithelium is flattened, so that the cavity of the alveolus is large. The lumen is usually filled with milk in these circumstances.

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